COMPLICATIONS—HYPOGLYCEMIA

Continuous Glucose Monitoring in Patients With or Without Symptoms of Hypoglycemia after Bariatric Surgery

CLARE LEE, TODD BROWN, MICHAEL SCHWEITZER, THOMAS MAGNUSON, JEANNE CLARK, Baltimore, MD

Objective: Hypoglycemia after bariatric surgery is an increasingly recognized metabolic complication. We sought to determine the sensitivity and specificity of a prior hypo-sx survey in detecting post-bariatric surgery hypoglycemia (PBSH) using a continuous glucose monitor (CGM).

Methods: Among the patients who underwent bariatric surgery at our institution and completed the hypo-sx survey, we enrolled 13 Roux-en-Y gastric bypass (RYGB, 7 with and 6 without hypo-sx) and 19 sleeve gastrectomy (SG, 9 with and 10 without hypo-sx) patients. Patients wore the CGM ( Dexcom, San Diego, CA) for 72-120 hours at home. Hypoglycemia was defined as postprandial interstitial glucose (IG) <54 mg/dl. We used Kruskal Wallis test to compare the difference in hypoglycemia across groups.

Results: A total of 19 patients (59%) had hypoglycemia (Table 1), with a mean low glucose of 46.8 mg/dl. Two patients reported hypo-sx. The prevalence of hypoglycemia did not differ by the type of surgery (69% vs. 53%) or the presence of hypo-sx by survey (63% vs. 56%). The survey had a specificity of 53.8% and sensitivity of 52.6% for measured PBSH.

Conclusions: Asymptomatic postprandial hypoglycemia was common in post-bariatric patients regardless of surgery type. Assessments that focus on hypoglycemic symptoms may not adequately capture PBSH. Future studies should consider CGM to assess the true prevalence and impact of PBSH.

Table 1. Baseline Characteristics and Results from Continuous Glucose Monitoring on Post-bariatric Surgery Patients Who Were Categorized as With or Without Symptoms of Hypoglycemia Based on Their Survey Responses.

<table>
<thead>
<tr>
<th>Group</th>
<th>RYGB (N=7)</th>
<th>SG (N=10)</th>
<th>P</th>
<th>RYGB Without hypo-sx (N=6)</th>
<th>SG Without hypo-sx (N=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age, years</td>
<td>52.9 ± 5.1</td>
<td>52.0 ± 10.8</td>
<td>0.71</td>
<td>41.9 ± 11.3</td>
<td>44.8 ± 11.9</td>
</tr>
<tr>
<td>% Female</td>
<td>67%</td>
<td>67%</td>
<td>0.60</td>
<td>66%</td>
<td>89%</td>
</tr>
<tr>
<td>% Caucasian</td>
<td>71%</td>
<td>67%</td>
<td>0.50</td>
<td>73%</td>
<td>60%</td>
</tr>
<tr>
<td>Time since surgery (years)</td>
<td>7.3 ± 2.2</td>
<td>4.8 ± 1.3</td>
<td>0.77</td>
<td>4.7 ± 0.7</td>
<td>4.2 ± 0.8</td>
</tr>
</tbody>
</table>

Percent Patients with Postprandial Hypoglycemia (N)

<table>
<thead>
<tr>
<th>Group</th>
<th>Total Average IG (mg/dL, SD)</th>
<th>Average Minimum IG (mg/dL, SD)</th>
<th>Postprandial Minutes/day &gt; 54 mg/dL (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RYGB</td>
<td>97.0 ± 8.7</td>
<td>47.0 ± 15.0</td>
<td>9.5 ± 2.7</td>
</tr>
<tr>
<td>SG</td>
<td>103.5 ± 12.5</td>
<td>46.5 ± 4.5</td>
<td>10.7 ± 2.0</td>
</tr>
</tbody>
</table>


Real-World Risk Indicators of Severe Hypoglycemia in T2D—Results of the InHypo-DM Study

ALEXANDRIA RATZKI-LEEWING, STEWART HARRIS, SELAM MEQUANINT, NATALIE H. AU, JASON E. BLACK, SONJA M. REICHERT, JUDITH B. BROWN, BRIDGET L. RYAN, London, ON, Canada

Insight into the self-reported frequency of third-party assisted severe hypoglycemia (SH) is critical for the therapeutic optimization of type 2 diabetes (T2D). This study presents real-world epidemiological evidence on the self-reported incidence and related risk indicators of SH.

A validated questionnaire (InHypo-DMPS) was administered to a population-based panel of adult Canadians with T2D treated with insulin and/or secretagogues. Questions pertained to respondents’ past hypoglycemia events as well as socio-demographic and clinical characteristics, including hypoglycemia unawareness. Univariable analyses (p≤0.20) followed by a multivariable zero-inflated negative binomial (ZINB) analysis were performed to explore the influence of potential risk indicators on the occurrence of any and repeated SH events.

The current evaluation is based on a cohort of 436 respondents (mean age: 53 years; male: 54%). Among these individuals, 37.8% (95% CI: 33.3%-42.4%) self-reported at least one SH event in the past year, the incidence rate was 2.4 events (95% CI: 2.26-2.55) per person-year. Based on the ZINB analysis, only non-severe (NH) hypoglycemia was independently associated with SH, holding other indicators constant. Among respondents who reported ≤1 [vs. zero] NH events, the odds of never experiencing an SH event decreased by 82% (95% CI: 39.3%-94.7%, p<0.006). Likewise, a history of NH, among those who had a chance of experiencing SH, increased the expected rate of SH by a factor of 4.29 (95% CI: 2.25-8.17, p<0.001).

Real-world estimates of SH in T2D are often limited by sub-optimal reporting and gaps in clinical practice. To help clarify the true frequency of SH, this large, population-based study leveraged the value and clinical relevance of self-reported hypoglycemia data. The results of this study suggest that the burden of third-party assisted SH is substantial in people with T2D. Clinical strategies to prevent NH may reduce the risk of any/repeated SH events and result in sequelae.

Supported By: Sanofi Canada

Correlates of Hypoglycemia among Youth with Type 1 Diabetes (T1D) and Suboptimal Glycemic Control

ANNA R. KAHLOSKA, JAMIE CRANBELL, KIMBERLY A. DRISCOLL, MICHAEL R. KOSOROK, DAVID M. MAANS, ELIZABETH J. MAYER-DAVIS, Chapel Hill, NC, Aurora, CO, Stanford, CA

Hypoglycemia is a major challenge of T1D. We examined the prevalence and correlates of hypoglycemia assessed by 7-day blinded continuous glucose monitoring on baseline at 233 youth with hemoglobin A1C (HbA1C) of 8.13% per inclusion criteria in the Flexible Lifestyles Empowering Change trial. The sample was 76.1% non-Hispanic white and 48.9% female with mean age 14.9±1.1 years and mean T1D duration 6.4±3.7 years. Mean HbA1c was 9±±1.2%. Over 7-days, 85.4% of youth experienced hypoglycemia (i.e., time ≤70 mg/dL and ≤54 mg/dL, an average of 32.5±37.3 min/day). 62.7% of youth experienced clinically serious hypoglycemia (i.e., time ≤54 mg/dL; an average of 24.5±40.5 min/day). Duration of hypoglycemia was inversely associated with HbA1c (Figure). In logistic regression modeling, sex, race/ethnicity, T1D duration, body mass index z-score (BMZ), fear of hypoglycemia (from the Hypoglycemia Fear Survey) and diabetes adherence (from the Diabetes Self-Management Profile-Self Report) were not associated with hypoglycemia. Youth with higher HbA1c were less likely to experience hypoglycemia (for a 1% higher HbA1c, odds ratio (OR) for clinical hypoglycemia: 0.52, 95% CI 0.39, 0.68; OR for clinically serious hypoglycemia: 0.59, 95% CI 0.43, 0.77). The data suggest that hypoglycemia is common among youth with elevated HbA1c and and guidance to limit hypoglycemia should be part of care in these patients.

Supported By: National Institutes of Health

A validated questionnaire (InHypo-DMPS) was administered to a population-based panel of adult Canadians with T2D treated with insulin and/or secretagogues. Questions pertained to respondents’ past hypoglycemia events as well as socio-demographic and clinical characteristics, including hypoglycemia unawareness. Univariable analyses (p≤0.20) followed by a multivariable zero-inflated negative binomial (ZINB) analysis were performed to explore the influence of potential risk indicators on the occurrence of any and repeated SH events.

The current evaluation is based on a cohort of 436 respondents (mean age: 53 years; male: 54%). Among these individuals, 37.8% (95% CI: 33.3%-42.4%) self-reported at least one SH event in the past year, the incidence rate was 2.4 events (95% CI: 2.26-2.55) per person-year. Based on the ZINB analysis, only non-severe (NH) hypoglycemia was independently associated with SH, holding other indicators constant. Among respondents who reported ≤1 [vs. zero] NH events, the odds of never experiencing an SH event decreased by 82% (95% CI: 39.3%-94.7%, p<0.006). Likewise, a history of NH, among those who had a chance of experiencing SH, increased the expected rate of SH by a factor of 4.29 (95% CI: 2.25-8.17, p<0.001).

Real-world estimates of SH in T2D are often limited by sub-optimal reporting and gaps in clinical practice. To help clarify the true frequency of SH, this large, population-based study leveraged the value and clinical relevance of self-reported hypoglycemia data. The results of this study suggest that the burden of third-party assisted SH is substantial in people with T2D. Clinical strategies to prevent NH may reduce the risk of any/repeated SH events and result in sequelae.

Supported By: Sanofi Canada

Figure: Average Minutes per Day of Clinical Hypoglycemia and Clinically Serious Hypoglycemia among Youth with T1D in two flexible lifestyles empowering change trials (n=233), plotted by hemoglobin A1C. Clinical hypoglycemia defined as duration of time ≤70 mg/dL and ≤54 mg/dL, over 7-day period of blinded continuous glucose monitor (CGM) wear time. Clinically serious hypoglycemia defined as duration of time ≤54 mg/dL over the 7-day blinded CGM wear time.
Does Hypoglycemia Awareness Status on Gold and Clark Questionnaires Predict Hormonal and Symptomatic Responses to Hypoglycemia (HG) in Type 1 Diabetes (T1D)?

NATHAN RUBIN, AMIR MOHIEET, LYNN E. EBERLY, ANJALI KUMAR, SILVIA MANGIA, ELIZABETH R. SEAGUIT, Minneapolis, MN

Hypoglycemia awareness (IAH) is characterized by the diminished ability to perceive symptoms of HG. Gold and Clark questionnaires are commonly used in research to identify patients with IAH. However, the relationship between IAH status on questionnaires and the symptom and counterregulatory (CR) hormone responses to HG are not well understood. In this study, we examined data from 51 research subjects with T1D who completed both questionnaires and underwent a hyperinsulinemic hypoglycemic clamp (target glucose 50 mg/dL) on the same day. Clarke and Gold scores were highly correlated with one another (r = 0.78) and each had a similar relationship with epinephrine (EPI) response during HG. Clarke r = -0.46, Gold r = -0.53 and symptom response (Clarke r = -0.80, Gold r = -0.52). However, Clarke and Gold disagreed on classification of HG awareness status (misclassification=37%, Cohen’s κ=0.54). Clarke classifications were: 26 Aware (A), 13 Indeterminate (I), 12 Unaware (U), whereas Gold classifications were 16 A, 15 I, and 20 U. A mixture model based clustering identified 3 patterns in joint and symptom responses. Cluster 1 subjects (n=10) had low symptom (<5) and EPI responses (<140) to HG and 8/10 were classified as U by one or both questionnaires. Cluster 3 subjects (n=9) had high symptom (20+) and EPI responses (450+) to HG and 8 of 9 were classified as A by one or both questionnaires. Cluster 2 subjects (n=22) had intermediate symptom and EPI responses to HG but concordance of classification by Clarke and Gold was true for only 11 of the 24. Clarke classified cluster 2 subjects as 12 A, 7 I, and 3 U whereas Gold classified the same subjects into 6 A, 7 I, and 9 U. IAH classification may be discordant between Clark and Gold questionnaires and may not always correlate with the CR responses during experimental HG. To ensure reproducibility, researchers must be rigorous and consistent in defining the awareness status of study subjects.

Supported By: National Institutes of Health

Impact of Aging on Risk of Hypoglycemia in Patients with Type 1 Diabetes

MEDHA MUNSHI, CHRISTINE SYLVE, ASTRID ATAKOV-CASTILLO, JORDAN DIABETES, JORDAN GREENBERG, TORI GREAVES, SAM P. CARL, ELENA TOSCHI, Boston, MA

Background: As T1D patients routinely reach older age, more information is needed to understand the impact of aging on the risk of hypoglycemia and its interaction with other age-related issues.

Methods: We evaluated 2 groups of patients with T1D: older (age ≥65 years) and younger (age 18-35 years). All patients were subjected to either BB (insulin glargine) or basal insulin (insulin detemir) therapy. The average age was 70 vs. 28 years; diabetes duration 36 vs. 7.7 years) and younger (age 18-35 years). All patients were subjected to either BB (insulin glargine) or basal insulin (insulin detemir) therapy. The average age was 70 vs. 28 years; diabetes duration 36 vs. 7.7 years.

Results: We evaluated 56 patients with T1D, 23 in the older and 33 in the younger group. The average age was 70 vs. 28 years; diabetes duration 36 vs. 14 years; A1C 8.0% vs. 7.9%, respectively. Clinically significant hypoglycemia (glucose ≤54 mg/dL for >15 min) occurred equally in 91% of older (mean 28 minutes/day) and 88% of younger (mean 23 mins/day) patients. Older patients reported hypoglycemia unawareness more (39% vs. 30%), with similar scores on HSF II (04 vs. 33). However, 61% of older patients with cognitive impairment (MoCA score <26) compared to 12% in younger adults. There was a higher comorbidity burden in older patients (average number of comorbidities 4 vs. 1), with a higher number of daily medications (10 vs. 4).

Conclusion: The risk of hypoglycemia is similar in older and younger patients when the comorbidity burden is taken into account. Cognitive dysfunction and polypharmacy may increase the risk of poor outcomes due to hypoglycemia.

Hospitalization and Emergency Department Visits for Severe Hypoglycemia among U.S. Adults with Diabetes and Serious Comorbid Conditions

ROZALINA G. MCCOY, HOLLY VAN HOUTEN, KASIA J. LIPSKA, NILAY SHAH, Rochester, MN, New Haven, CT

Diabetes care guidelines recommend more relaxed glycemic targets for patients with specific chronic conditions because they are thought to have an increased risk of hypoglycemia, limited life expectancy, and/or high clinical complexity. These include dementia, end stage renal disease (ESRD), stages 3-4 chronic kidney disease (CKD), myocardial infarction, heart failure, cerebrovascular disease, chronic obstructive pulmonary disease, cancer, arthritis, urinary incontinence, falls, depression, hypertension, cirrhosis, proliferative retinopathy, and peripheral neuropathy. The rates of severe hypoglycemia among patients with these conditions are unknown. We quantified rates of hospital and emergency department care for hypoglycemia among 216,639 adults (mean 65.5 years old) with diabetes in 2015 using the OptumLabs Data Warehouse (administrative database of >100 million commercially-insured and Medicare Advantage beneficiaries). Hypoglycemia rates varied widely: 10.2/1000 person-years (PY) in patients with hypertension, 26.9/1000 PY with CKD, 26.8/1000 PY with cirrhosis, 37.7/1000 PY with dementia, and 58.3/1000 PY with ESRD. Hypoglycemia was rare among patients with no conditions (2.0/1000 PY). After adjustment for all conditions, prior hypoglycemia, age, sex, race, HbA1c, and diabetes medications, the risk of severe hypoglycemia was significantly increased for all conditions except arthritis, incontinence, and cancer. Hypoglycemia risk increased rapidly with the number of comorbidities: OR 1.8 (95% CI 1.4, 2.2) for 2 conditions, 7.7 (6.2, 9.6) for 5, 16.6 (13.1, 21.1) for 7, and 25.6 (30.4, 32.3) for ≥8 conditions compared with ≤1 condition. Severe hypoglycemia is common among patients with chronic conditions. Rates vary between conditions but increase dramatically in patients with multiple comorbidities. These data can help inform decisions about glucose-lowering therapy for patients with comorbidities.

Supported By: National Institute of Diabetes and Digestive and Kidney Diseases (K23DK114497)

Beta-Blocker Usage and Hypoglycemia in Hospitalized Patients with Diabetes Mellitus

JENNIFER MERRILL, KATHLEEN M. DUNGAN, Columbus, OH

Background: Although β-blockers (BB) theoretically increase the risk of severe or prolonged hypoglycemia, studies have suggested that BB may decrease the risk of hypoglycemia-associated arrhythmias and death. However, there is little evidence in hospitalized patients on insulin.

Aim: To determine the relationship between BB use and incidence of hypoglycemia and mortality in hospitalized patients.

Methods: We retrospectively identified non-critically ill hospitalized patients receiving subcutaneous insulin and undergoing bedside glucose monitoring over a 2 year period. BB and basal insulin use were identified on the admission medication list. Hypoglycemia, defined as any glucose <70 mg/dL within 24 hours of admission (Hypo24) or throughout the hospitalization (HypoT) and any glucose <40 mg/dL throughout the hospitalization (Hypo40) were compared between patients with and without BB.

Results: 13,424 patients were included, with 2648 patients receiving a BB at admission (19.7%). After controlling for other variables, the odds of Hypo24, HypoT, and Hypo40 were higher for BB recipients (Hypo24 OR 3.79, 95% CI 2.1-6.4, p<0.0001, fully adjusted model; HypoT OR 7.79, 95% CI 6.7-8.7, p<0.0001, fully adjusted model; Hypo40 OR 1.95, 95% CI 1.41-2.67, p<0.0001). However, there was a significant interaction across basal insulin usage, with increased odds of Hypo24 and Hypo40 among basal insulin non-users but not basal insulin users. Hypo24, HypoT, and Hypo40 were associated with increased mortality in adjusted models. There was evidence of an interaction by BB status in the relationship between Hypo40 and mortality (with increased mortality among non-users but not users), but not at other time points.

Conclusions: BB use is associated with higher risk of hypoglycemia in hospitalized basal insulin non-users, but not basal insulin users. Hypoglycemia is associated with increased hospital mortality, regardless of BB use, but early hypoglycemia-associated mortality risk is attenuated by BB use.

Supported By: National Center for Research Resources (UL1RR025759), National Institutes of Health (K23DK080891, R21DK081877)

Inadequate Use of Glucagon in Patients with T1D

MOREY W. HAYMOND, JINDWEN LIU, JEOFFREY BISPHAM, AILEEN HICKEY, ALICIA H. MCAULIFFE-FOGARTY, Houston, TX, Boston, MA

Glucagon is an invaluable tool for patients with type 1 diabetes (T1D) who experience severe hypoglycemia, but little is known about the actual use of glucagon in this patient population. This study uses data from individuals with T1D or caregivers to assess the perceptions and/or past experiences using the currently available glucagon rescue kits, and factors that might increase its utility in the management of T1D. Survey responses from 264 adults with T1D (mean age 41.2 years (SD 15.5)) and 58 caregiv-
ers of a person with T1D (mean age 11.8 years [SD 3.7]) were included in the analyses. Overall the participants were highly educated, predominantly covered by private health insurance, and the majority were on insulin pumps. The survey revealed that the majority of the individuals with T1D had been prescribed glucagon, however, almost a third of the adult patients did not receive any education on its use, and a third of the adult patients did not have a current prescription. Caregivers reported higher percentages of receiving education on glucagon use and also having a current prescription. Of those with severe hypoglycemia who had glucagon available, half did not receive a glucagon injection. The majority of patients who had received glucagon injection reported various problems with the procedure; those who did not receive glucagon injection reported a number of barriers to its use. These data strongly suggest the need for 1.) standards of practice that would increase prescribing of glucagon 2.) initial and ongoing education on its use and administration 3.) development of a glucagon rescue option that would eliminate the complexity relating to current formulations and packaging of rescue glucagon kits.

Supported By: Zealand Pharma A/S

384-P Factors Associated with Severe Hypoglycemia among Patients with Type 2 Diabetes Treated with Insulin MANJU PAWASKAR, JINAN LIU, R. RAVI SHANKAR, SWAPNIL RAJPATHAK, North Wales, PA, Rahway, NJ

We have previously reported that rates of severe hypoglycemic events (SHEs), defined as events that required hospitalization or an emergency department visit) are higher in patients with type 2 diabetes (T2D) on insulin alone (3.4%) or in insulin+SU (2.5%) compared to those on insulin+other anti-hyperglycemic agents (AHA).[1,6]. The present analyses were conducted to further evaluate the independent risk factors of SHE after accounting for differences in two treatment groups based on propensity for SHE: Insulin+SU and Insulin+Other AHA. This retrospective analysis using MarketScan database included T2D adults (n=20,147; mean age: 54.0 years; 53% females) with a first prescription of insulin from 1/1/2013 to 12/31/2013 (index period). The database was measured from the index date to the end of follow-up (12/31/2013). Multivariable Poisson regression was performed to compare the risk of SHE between insulin+SU vs. insulin+other AHA users and assess other predictors. The unadjusted SHE rate per 100 person years was 2.8% among those on insulin+SU and 1.3% among those on insulin+other AHA. After adjusting for patient’s baseline characteristics, the risk of SHE was 84% higher in patients on insulin+SU compared to those on insulin+other AHA [Hazard ratio (HR):1.84; 95% confidence interval (CI): 1.68-2.01]. In addition to the treatment type, other factors predictive of SHE were previous history of SHE (HR: 4.73; 95% CI: 4.33-5.17), and history of comorbidities including chronic kidney disease (HR: 1.75; 95% CI: 1.50-1.92), cardiovascular disease (HR: 1.60; 95% CI: 1.48-1.76), and neurophathy (HR: 1.55; 95% CI: 1.43-1.69). Our results suggest the risk of SHE is lower in patients on insulin with other AHA compared to patients on insulin alone or with SU. Healthcare professionals should take into account the risk of having SHE while making treatment choices especially for vulnerable populations such as patients with prior history of SHE, and other comorbidities.

Supported By: Merck & Co, Inc.

Impact of Switching from Sulfonylureas to Dipeptidyl Peptidase-4 Inhibitors on Hypoglycemia Burden in the United States—A Predictive Modeling Approach JINAN LIU, YUEXIN TANG, HAKIMA HANNACHI, SAMUEL S. ENGEL, SWAPNIL RAJPATHAK, North Wales, PA, Kenilworth, NJ

Hypoglycemia requiring medical care represents significant burden for patients with T2DM and health systems. Therefore, minimizing risk of hypoglycemia needs to be considered in treatment decision making, in addition to attaining glycemic goal. Using a predictive modeling approach, we conducted a study to estimate reduction in hypoglycemia event rates and costs that may result from switching from sulfonylureas (SU) to dipeptidyl peptidase-4 inhibitors (DPP-4i) in the United States.

A large commercial claims database was used to identify adult T2DM patients newly treated with SU or DPP-4i in 2014. Rates and costs of hypoglycemia were assessed within one year after drug initiation. A Poisson model, built and developed based on DPP-4i users, was applied in SU users to estimate hypoglycemia rate if they had been switched to DPP-4i adjusting for patient demographics, comorbidities and medication use at baseline. Using National Health and Nutrition Examination Survey, the observed and predicted hypoglycemia costs were then projected on the national level for SU users, and the cost difference represented the change of total hypoglycemia costs had they switched to DPP-4i instead on the national level. Among patients who initiated SU (n=38,913) and DPP-4i (n=23,956), average age was 52 years; 44% were female. The observed hypoglycemia rates per 100-person years were 6.4 (95% CI: 6.0, 6.9) and 10.6 (95% CI: 10.1-11.1) in DPP-4i and SU groups, respectively. The predicted rate of hypoglycemia was 6.4 (95% CI: 6.1-6.8) in SU group had they switched to DPP-4i. At a national level, this switching could result in potential costs savings of $586 million (from $699 million to $113 million) within one year period.

Our study suggests that switching patients from SU to DPP-4i could reduce hypoglycemia event rates by almost 40% and also result in substantial cost savings associated with hypoglycemia in the United States.

Supported By: Merck & Co, Inc.

Heart Rate Variability in Patients with Type 1 Diabetes and Hypoglycemia with Different Control of Diabetes Mellitus KATERYNA MOSHENETS, NATALIIA PERTSEVA, Dniprop, Ukraine

Background and Aims: To study the correlation of heart rate variability (HRV) in patients with type 1 diabetes mellitus (T1DM) depending on glucose control and hypoglycemia.

Materials and Methods: The study involved 87 patients with T1D, including 45 men (52%), women - 42 (48%). The average age of patients - 26.6±1.48 years, disease duration 11.6±1.42 years, BMI: 23.2±0.63 kg/m². All patients used basic-bolus insulin therapy with daily dose of Units 45±2.26. All patients were conducted with Continuous Glucose Monitoring System (CGMS) and 24-Hour Holter Monitoring (HM) in same time. Echocardiography was used to exclude organic pathology of the heart. Patients were divided to groups according to HbA1c: Group 1 had HbA1c<7, 5%; group 2 had HbA1c≥7, 5%, and subgroups: A-without hypoglycemia, B-with hypoglycemia.

Results: Groups did not differ in the frequency of hypoglycemia. Calculation of results depending on the duration T1DM showed an increase LF/HF (n=0.472; p<0.05). Groups differed significantly according to the following frequency characteristics of heart rate such as VLF, LF, HF (p<0.05).

The groups did not differ in other factors. In Group 2B as compared to 2A identified decrease such time-domain indicators of HRV: RMSSD 22.8 ms (15.0; 36.0) vs. 32.6 ms (27.0; 43.0); pN50 daily 3.50% (1.0; 10.0) vs. 8.50% (6.00-13.50) and daily frequency characteristics HRV: HF 380.0 ms² (149.0; 715.0) to 719.0 ms² (475.0; 1153.0) and increased LF/HF 4.5; (4.10; 6.50) vs. 3.30 (2.90; 4.30). All findings are significant (p<0.05). A similar pattern was observed in patients in 1st group.

Conclusions: HRV is lower in patients with bed glucose control (HbA1c≥7, 5%). The most reliable criteria for assessing changes in HRV are in patients with T1DM are RMSSD, LF, HF and LF/HF are. Hypoglycemia is the most significant factor that reduces the HRV.

Limited Availability of Glucagon by Emergency Personnel PETER KAHN, NICOLE WAGNER, ROBERT A. GABBAY, New Haven, CT, Boston, MA

Hypoglycemia causes more than 100,000 emergency department visits per year costing over $120 million. Glucagon can reduce the number and severity of hypoglycemic episodes requiring emergency medical attention and hospital admission. However, EMS personnel are often unable to administer glucagon.

U.S. EMS offices were queried for glucagon administration and blood glucose testing protocols. Only paramedics are able to administer glucagon in most states, whereas the 198,200 EMT-Basics personnel nationally cannot. The average response time to calls was 15.34 minutes. Dispatchers correctly coded 44.67% of these calls as a “diabetic problem,” increasing the likelihood of dispatching providers who cannot administer glucagon. The National Emergency Management Information System (NEMIS) (2012: 2015) indicates 89,263 cases in which glucagon was administered with only 3,944 instances.

Despite its favorable safety profile, glucagon cannot be administered by EMT-basics in most states, even though family members can often with minimal training. 3 out of 4 emergency personnel are unable to use glucagon. The likelihood of the correct personnel being dispatched based on dispatcher information alone is poor. Increasing the availability of glucagon in the prehospital setting will likely result in reduced cost burden and adverse consequences of severe hypoglycemia.
Effect of Hypoglycemia during Intensive Insulin Therapy on Long-Term Glycemic Control in Patients with Newly Diagnosed Type 2 Diabetes

LIUJIAN XU, YANBING LI, Guangzhou, China

Aims: Short-term intensive insulin therapy induces long-term drug-free euglycemic remission in half of patients with newly diagnosed type 2 diabetes mellitus (T2DM) but causes an increased risk of hypoglycemia. Studies identifying the impact of hypoglycemia are necessary.

Methods: We analyzed data from three randomized prospective trials conducted at our institution from 2002 to 2015. A continuous subcutaneous insulin infusion (CSII) was provided to achieve the glycemic goals and then maintained for 14 days.

Results: Patients who attained one-year drug-free glycemic remission were younger (48.06±9.85 vs. 50.95±11.70 years, P=0.037) and had a higher body mass index (BMI) (25.53±3.52 vs. 24.66±3.20 kg/m², P=0.046) than those who did not. Notably, the median number of episodes of mild hypoglycemia with nadir glucose values of 3.0-3.9 mmol/L was higher in the remission group than in the non-remission group (5 (6) vs. 2 (5), P=0.001). However, the number of episodes of clinically significant hypoglycemia (<3.0 mmol/L) was insignificantly lower in the remission group (0 (1) vs. 0 (1), P=0.723). Patients with higher glucose levels (glycated hemoglobin (HbA1c), fasting plasma glucose (FPG) and postprandial glucose (PPG)) and lower β-cell functions (homeostasis model assessment of β-cell function (HOMA-B)) at baseline faced a greater risk of clinically significant hypoglycemia (OR=2.02, 95% CI 1.40-2.92, P<0.001). According to the logistic regression analysis, mild hypoglycemic episodes were positively and independently related to long-term glycemic remission.

Conclusions: Mild hypoglycemic episodes during CSII therapy are related to better long-term drug-free glycemic remission in patients with newly diagnosed T2DM. However, clinically significant hypoglycemia is not correlated and should be avoided.

IDegAsp Improves Glycemic Control with Minimal Hypoglycemia—An Indian Real-World Study in T2D Subjects

JOHTHYDEV KESAVADEV, BANSHI D. SABOO, ARUN SHANKAR, ASHWIN DAVID, ROHIT WARRIER, GOPKA KRISHNAN, LAKSHMY RAMACHANDRAN, SUNITHA JOHTHYDEV, Trivandrum, India, Ahmedabad, India, Kochi, India

Background: IDegAsp is the first insulin co-formulation constituting 70% insulin degludec and 30% insulin aspart. In contrast to conventional premix analogues, degludec component of IDegAsp lowers variability, fasting glucose with comparable glycemic control and fewer hypoglycemic events. Re-suspension errors inherent to premix analogues also does not occur with IDegAsp. In routine diabetes practice, patients have customised A1c goals depending on the associated comorbidities and risk factors.

Aim: To assess the safety and efficacy of IDegAsp in Indian T2D subjects in a real-world setting.

Methods: T2D initiated on IDegAsp and on regular follow-up were de-identified from EMR. Clinical outcomes and hypoglycemic events were captured. n= 152, age= 52.9±11.9 y, diabetes duration= 11.5±13.8 y, 78.57% males, treatment duration= 10.3±6.5 mths.

Results: 92% of the patients achieved customised A1c targets. Reduction from baseline: 0.91% in A1c (p=0.0004), 41.4 mg/dL in FBS (p<0.0001), 0.80 kg in body weight (p=0.0083). Five hypoglycemic episodes were reported (none severe). There were no reported episodes of nocturnal hypoglos.

Conclusion: In this real-world study involving T2D subjects in India, IDegAsp improved HbA1c and FBS significantly, with less hypoglycemia and no weight gain. Some of these outcomes are contrary to those reported in clinical trials and could have resulted from the new combination oral therapies.
the risk of nocturnal hypoglycemia in patients with type 1 diabetes (T1D) or type 2 diabetes (T2D). This post-hoc analysis investigated the proportion of patients with T1D or T2D treated with degludec or glargine U100 meeting the ADA recommended upper limit of the pre-mea glucose goal of <130 mg/dL (<7.2 mmol/L) at each visit (start and end of 16 week maintenance) without noctural hypoglycemia. Patients with T1D or T2D and with FPG measurements during the 16-week maintenance period of the SWITCH 1 (n=501) and SWITCH 2 (n=720) trials (randomized, double-blind, crossover, treat-to-target trials of patients treated with degludec or glargine U100) were included. Nocturnal hypoglycemia was defined as any blood glucose confirmed (<56 mg/dL [<3.1 mmol/L]) symptomatc event occurring from 00:01-05:59 in the SWITCH trials, significantly more patients with T1D or T2D treated with degludec achieved FPG target during the maintenance period, and did so without nocturnal hypoglycemia, compared with glargine U100 (Figure 1).

In conclusion, compared with glargine U100, treatment with degludec was associated with greater opportunity to reach target FPG without an increased risk of nocturnal hypoglycemia.

Figure 1. Proportion of patients meeting American Diabetes Association recommended FPG target (<130 mg/dL [<7.2 mmol/L]) without nocturnal hypoglycemia in the 16-week maintenance period in the SWITCH 1 and 2 trials.

<table>
<thead>
<tr>
<th></th>
<th>% (number of patients) meeting FPG target</th>
<th>Odds ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within FPG target</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine U100</td>
<td>6.6 [1.1; 22.8]**</td>
<td>(131) (94)</td>
</tr>
<tr>
<td>Degludec</td>
<td>1.95 [133; 2.84]**</td>
<td>(92) (57)</td>
</tr>
<tr>
<td>Within FPG target &amp; without nocturnal hypoglycemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine U100</td>
<td>1.37 [1.06; 1.76]**</td>
<td>(401) (361)</td>
</tr>
<tr>
<td>Degludec</td>
<td>1.45 [1.14; 1.85]**</td>
<td>(356) (303)</td>
</tr>
</tbody>
</table>

In favor of glargine U100 In favor of degludec

Support by: Novo Nordisk

Hypoglycemia in Patients with Diabetes in an Australian Public Hospital Setting

MILAN K. PIYA, REETU ZARORA, THERESE FLETCHER, DAVID SIMMONS, Campbelltown, Australia

Background: Diabetes is a common co-morbidity among hospital inpatients, particularly in medical wards. Diabetes is linked to increased length of stay and mortality in hospital inpatients, and hypoglycemia (hyp) is considered a contributory factor. We sought to determine the prevalence of diabetes in medical wards and the prevalence and patterns of hyp during their hospital stay.

Methods: A daily census on three medical wards (79 beds) was conducted over a 4 month period from June 2017 in a 306 bed tertiary Sydney hospital. Charts and medications for inpatients with diabetes were audited each Friday using a questionnaire based on the UK National Diabetes Inpatient Audit. Patients admitted under the care of the diabetes team were excluded. Readmissions were counted as separate events.

Results: The mean prevalence of diabetes was 27%, of which 2.4% had T1DM, with 212 patient episodes audited in 196 patients (16 readmissions). Mean age (SD) was 71 years (11.2), 54% male. Only 5.6% had a diabetes type 1 (T1DM), with 212 patient episodes audited in 196 patients (16 readmissions).

Audit. Patients admitted under the care of the diabetes team were excluded. There were 74 events of hypo (<72 mg/dL) in 38 patients (18%), with 10 episodes of severe hypo (<54 mg/dL) in 9 patients (4.3%). Within the first week of admission, 50 of these hypo events occurred (8 severe) in 29 patients. insulin was prescribed in 82% of the patients who had hypo (31/38), and 69% of those who had severe hypo (8/8), with only 50% of them admitted on insulin. A smaller number of hyp events occurred 8am-5pm compared to 5pm-9am (29 vs. 45), with no significant difference between days of the week.

Conclusion: Hypoglycemia is a major burden in patients with diabetes in hospital, particularly in the first week of admission, even when patients are not admitted due to diabetes related problems. Insulin use was the major risk factor and many patients had multiple hypo events. We recommend early involvement of the diabetes inpatient team as well as centralized point of care testing of glucose to allow early identification of patients at risk.

393-P

Insulin Acts in Ventromedial Hypothalamus to Regulate the Sympathoadrenal Response to Hypoglycemia in Rats

RAHUL AGRAWAL, ADRIANA VIERA DE ABREU, GRIFFIN T. DURUPT, SIMON J. FISHER, Salt Lake City, UT

We tested the hypothesis that the correction of ventromedial hypothalamic (VMH) insulin deficiency was sufficient to restore the impaired sympathoadrenal response to hypoglycemia in diabetic rats. Sprague-Dawley rats were injected with either vehicle (nondiabetic controls; CON) or streptozotocin (STZ; 85 mg/kg IP). STZ diabetic rats received osmic mini-pumps to infuse either artificial cerebrospinal fluid (DIAB) or insulin (3mU/d; DIAB+ins/MHV) into the VMH bilaterally. Two weeks later, all three groups underwent hyperinsulinemic (50 mU/kg.min) hypoglycemic (~50 mg/dl) clamps. As expected, STZ-diabetic rats showed blunted epinephrine response to hypoglycemia as compared to nondiabetic controls. Chronic infusion of insulin into VMH of diabetic rats normalized the epinephrine response to hypoglycemia and lowered the glucose infusion rate required to maintain hypoglycemia. Examining brain insulin action, it was noted that VMH of diabetic rats had decreased Akt phosphorylation and decreased expression of insulin dependent glucose transporter 4 (GLUT4) in VMH by 44% and 40% respectively as compared to the nondiabetic controls. Notably, chronic infusion of insulin to the VMH normalized Akt phosphorylation and GLUT4 expression.

In summary, insulin acts chronically in the VMH to preserve the sympathoadrenal response to hypoglycemia, possibly by regulating GLUT4 expression.

394-P

Somatostatin Receptor II Antagonism Improves Glucagon Counter-regulatory Responses to Recurrent Hypoglycemia in Male Sprague-Dawley Rats

MICHAEL RIDDELL, MAHSA JAHANGIRIESMAILI, ERIN R. MANDEL, CAYLEE A. GREENBERG, ADIBHE M. PASIEKA, TREVOR TEICH, OWEN CHAN, RICHARD T. LIGGINS, Toronto, ON; Canada, Salt Lake City, UT; Vancouver, BC, Canada

Glucagon [GCN] helps prevent hypoglycemia when blood glucose levels drop, however, recurrent hypoglycemia attenuates GCN counterregulation to subsequent bouts of hypoglycemia. As somatostatin normally inhibits GCN secretion, we tested the hypothesis that a somatostatin receptor type 2 antagonist (SSTR2a), PRL-2903, improves GCN responses attenuated by recurrent hypoglycemia in healthy rats. Male Sprague-Dawley rats (n=22) were made hypoglycemic on three consecutive days (days 1-3, blood glucose 1.7-2.2 mmol/L for ~2 h) via exogenous insulin administration (10-, 8- and 5- U/kg of Humulin-R on days 1-3, respectively). GCN levels dur-

p<0.05 vs. CON; #p<0.05 vs. DIAB

Supported by: ADA-Supported Research & Moderated Poster Discussion
rent hypoglycemia in counterregulatory failure. On day 4, rats were treated with either PRL-2903 (10 mg/kg IP, n=13) or vehicle (n=9) 1 h prior to the induction of hypoglycemia with 5 U/kg R-insulin. GCN levels during hypoglycemia (i.e., glucose ≤3.5 mmol/L) were 2.5-fold higher (109±5 vs. 44±26 pg/mL; P=0.004) compared to vehicle, and time to reach hypoglycemia was 3.2-fold longer (64±45 vs. 20±10 min; P=0.001), with PRL-2903 pre-treatment. Interestingly, C-peptide levels were also lower (P=0.001) with PRL-2903 (0.35±0.22 ng/mL), compared to vehicle (0.63±0.21 ng/mL), inferring a lower insulin secretion during hypoglycemia with PRL-2903 treatment.

In conclusion, our data suggests that SSTR2α improves GCN responses following recurrent hypoglycemia, and that this improvement may be associated with a reduction in insulin secretion in healthy rats. Therefore, SSTR2α treatment may be a useful therapeutic approach to improve GCN counterregulatory responses to hypoglycemia.

Supported By: JDRF, Zucara Therapeutics Inc.

A Novel Continuous Glucose Monitoring System Accurately Detects Existing and Impending Hypoglycemia

PETER CALHOUN, TERRI JOHNSTON, ANDREW BALO, DAVID A. PRICE, San Diego, CA

A200-P

Autonomous real-time continuous glucose monitors (rtCGM), unlike intermittently scanned continuous glucose monitors (isCGM), can proactively warn users of impending hypoglycemia. This study assessed the likelihood of realized hypoglycemia when an alert is triggered in the novel factory-calibrated rtCGM system (“G6 FC” Dexcom). Subjects wearing a G6 rtCGM participated in 1 to 3 in-clinic sessions where venous YSI plasma glucose measurements were sampled every 15 minutes. Three types of hypoglycemic alerts were assessed: “Low” (<70 mg/dL), “Urgent Low” (<55 mg/dL), and the new “Urgent Low Soon” (<55 mg/dL within 30 minutes). YSI glucose values were linearly interpolated to give estimated glucose values between YSI glucose measurements. The first “Low” and “Urgent Low” alerts were matched with actual and interpolated YSI values within ±15 minutes. The first “Urgent Low Soon” alerts were matched with actual and interpolated YSI values within 30 minutes after the alert. The Table shows 77% of “Low” alerts and 88% of “Urgent Low” alerts correctly warned of a hypoglycemic event (YSI reading below 70 mg/dL) within ±15 minutes. There were 480 “Urgent Low Soon” alerts, 86% of which correctly predicted a hypoglycemic event in the next 30 minutes. The G6 FC CGM System provides accurate alerts to patients who could facilitate actions to prevent or minimize hypoglycemia.

Table. Hypoglycemic Rates during a “Low” or “Urgent Low” Alert

<table>
<thead>
<tr>
<th>Type of alert</th>
<th>Number of alerts</th>
<th>Number of events with a nadir YSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low ≤70 mg/dL</td>
<td>185 (29.8%)</td>
<td>478 (77.1%)</td>
</tr>
<tr>
<td>Urgent Low ≤55 mg/dL</td>
<td>249 (63.7%)</td>
<td>353 (88.1%)</td>
</tr>
</tbody>
</table>

Machine Learning Identification of Multiple Predictively Equivalent Risk Models for Severe Hypoglycemia in Patients with Type 2 Diabetes

SISI MA, PAMELA SCHREINER, RACHEL ZMORA, ELIZABETH R. SEAQUIST, LISA S. CHOW, Minneapolis, MN

Severe hypoglycemia (SH), hypoglycemia requiring medical assistance and either blood glucose ≤50 mg/dL or glucose administration, instills fear in patients treated for diabetes. While risk models for SH may categorize an individual’s risk, incomplete or unavailable (“missing”) data limit clinical application. To circumvent the “missing” data issue, we used machine learning to identify multiple predictively equivalent risk models for SH in patients with type 2 diabetes (T2DM) data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study (n=10,251) were analyzed. Over ACCORD follow-up (mean 4.7± 1.4 years), 721 incident SH events were observed. We examined 95 candidate risk factors for model construction. Multiple predictively equivalent risk models (n=194) were induced using the SurvTIE* algorithm (an adaptation of TIE* algorithm to survival outcome) and with Cox regression and time-varying covariates. For each risk model, the number of risk factors ranged from 18-23 (median = 19). Unbiased performance estimations of c-index 0.78±0.03 were obtained from repeated cross-validation. Table 1 shows several unique models with equivalent predictive ability. In patients with T2DM, multiple predictively equivalent risk models for SH can be identified, potentially personalizing model selection when data are “missing.”

Table 1. Nine examples of unique models for SH in patients with Type 2 DM which are predictively equivalent

<table>
<thead>
<tr>
<th>c-index</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>0.79</td>
<td>0.78</td>
<td>0.79</td>
<td>0.79</td>
<td>0.79</td>
<td>0.79</td>
<td>0.79</td>
<td>0.79</td>
<td>0.79</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.78</td>
<td>0.79</td>
<td>0.78</td>
<td>0.79</td>
<td>0.79</td>
<td>0.79</td>
<td>0.79</td>
<td>0.79</td>
<td>0.79</td>
</tr>
<tr>
<td>Model 3</td>
<td>0.79</td>
<td>0.78</td>
<td>0.79</td>
<td>0.79</td>
<td>0.79</td>
<td>0.79</td>
<td>0.79</td>
<td>0.79</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Sustainability of a Real-Time Informatics Alert to Prevent Inpatient Severe Hypoglycemia

MICHAEL ELLIOTT, MARY C. BLACKBURN, KEVIN M. HEARD, PAUL E. MILLIGAN, PAULINA CRUZ BRAVO, GARRY S. TOBIN, St. Louis, MO, High Ridge, MO

Inpatient severe hypoglycemia (SH), blood glucose (BG) <40 mg/dL, is associated with morbidity. We previously piloted a predictive model to identify and intervene in inpatients at risk for SH that decreased the rate of SH by 68%. Expanding the alert system-wide to 9 hospitals, succeeded in reducing the occurrence of severe hypoglycemia from 2.9% to 1.7% per 1000 at risk patient days during all visits, and from 4.4% to 2.5% during visits where an alert occurred across all hospitals (both p-values<0.001). There were 4142 alerts in 2013; number increased to 5171 in 2014, and stayed steady in 2015 (5161), 2016 (5649), and 2017 (4984).

This study reflects a retrospective analysis of system-wide data from 2011 to 2017. Results show BG levels post alert are higher on average (mean 92.83) than pre-alert (mean 74.43). This magnitude of difference occurs in each year (pre-post differences range from 14.7 to 19.3), suggesting that the alert system led to a sustained beneficial effect over time. A decreasing trend in SH rate over time was observed, which differed by hospital (Figure). System-wide electronic surveillance and alerts improve safety in patients with diabetes across a range of clinical settings. This study proves ongoing efficacy of the alert process and variables.
of experiencing any event was not significantly associated with disclosure behaviour (p=0.08). However, the rate of repeated events was almost double (IRR=1.9, 95% CI: 1.2 to 3.0, p=0.004) among individuals who under-reported their SH as compared to those who did not. These results persisted after adjusting for age, medication type, income, most recent HbA1c, and presence of comorbidities. This population-based study revealed a nearly two-fold higher rate of SH among those who under-report to their HCP. Thus, HCPs should be aware that patient reporting may not be a true reflection of SH events and make efforts to elicit accurate information regarding SH events from their patients, especially for those at risk for repeated SH.

Supported By: Sanofi Canada

400-P
Clinical Outcomes and Mortality among Patients Hospitalized with Hyperglycemia and End-Stage Renal Disease in the U.S.

401-P
Decreasing Incidence of Postinsulin Hypoglycemia for Hyperkalemia Treatment

402-P
Decreasing Incidence of Postinsulin Hypoglycemia for Hyperkalemia Treatment

403-P
Acute and Chronic Complications

Table. Post-Insulin Hypoglycemia for Hyperkalemia Treatment.

Glycemic Control - Post-Insulin

<table>
<thead>
<tr>
<th>Hypoglycemia Orderset</th>
<th>01/01/16-03/19/17</th>
<th>03/01/17-05/31/17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperkalemia Orderset—Revision a (n=25)</td>
<td>21%</td>
<td>10%</td>
</tr>
<tr>
<td>Hyperkalemia Orderset—Revision b (n=146)</td>
<td>5%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Hypoglycemia (<70mg/dL) 21% 10%
Severe Hypoglycemia (<40 mg/dL) 5% 2%

Hypoglycemia in Insulin-Treated Type 2 Diabetes

Objective: Emerging evidence has suggested that glycemic variability plays an important role in the development of diabetes complications. We aimed to evaluate the influence of c-peptide levels on glycemic variability and hypoglycemia in patients with GAD-antibody negative, insulin-treated type 2 diabetes.

Methods: We enrolled 80 patients with insulin-treated type 2 diabetes (mean age 62.6 ± 9.4 years, mean HbA1C 71.9 ± 11.9 mmol/l, mean BMI 33.1 ± 5.7 kg/m²). All patients were GAD-antibody negative, had long diabetes duration (18.5 ± 7.4 years) and were treated with basal-bolus insulin. Glycemic variability and hypoglycemia duration were assessed from continuous glucose monitoring data recorded over 8 consecutive days. Glycemic variability was assessed by calculating mean Coefficient of Variation (CV). Hypoglycemia was defined as BG ≤70 mg/dl (3.9 mmol/L) or BG ≤54 mg/dl (3.0 mmol/L). Fastig c-peptide and fasting glucose were measured on day 1.

Results: Mean fasting c-peptide was 847 ± 493 pmol/L. Low levels of fasting c-peptide were correlated to higher CV (r = -0.44, P=0.001). In a multivariate regression model with HbA1C, BMI, diabetes duration and total daily insulin dose only c-peptide was significantly associated with CV. 47.5% of the patients had at least one episode of hypoglycemia (BG ≤70 mg/dl) and 23.7% had at least one episode of BG ≤54 mg/dl. Patients with at least one episode of hypoglycemia had significant lower c-peptide than patients without hypoglycemia (494 ± 460 pmol/L vs. 821 ± 479 pmol/L, P=0.004). There was no significant difference in c-peptide between patients with BG ≤70mg/dl and patients with BG ≤54mg/dl.

Conclusion: Low levels of c-peptide are associated with higher glycemic variability and risk of hypoglycemia in GAD-antibody negative patients with insulin treated type 2 diabetes, suggesting a role for c-peptide in optimizing treatment and prevention of hypoglycemia in insulin-treated type 2 diabetes.
**402-P**

**Increased Fluctuation of Measured Glucose in Critically Ill Patients Is an Independent Predictor of Mortality**

NAGA SASIDHAR KANAPARTHY, SHERIN ELSA MATHEWS, KAMALA RANYA KALLUR, Valhalla, NY, Jersey City, NJ, New York, NY

Background: Extremely high glucose values in critically ill patients have been studied and shown to be predictors of mortality. In addition, glucose fluctuation is also proposed to have been a determinant of poor outcome. In our study, we attempt to understand whether there is a relation between the fluctuations of glucose in critically ill patients to their mortality.

Methods: Data was obtained from “Medical Information Mart for Intensive Care III” database between 2001 and 2012. Fluctuation was measured as coefficient of variance of glucose (CVG). Patients were split into four groups based on the CVG of glucose levels during their ICU stay, namely Group 1: <25%, Group 2: 25%-50%, Group 3: 50%-100% and Group 4: >100%. Outcomes were measured at 3-day mortality interval and the relative risk was compared across the four groups. Multinomial logistic regression with length of stay, prednisone administration and Simplified Acute Physiology Score (SAPS) II as variables were run to assess the relative risk ratios (RRR) of increased CVG with mortality.

Results: A total of 45,302 adult ICU admissions were considered, 82.1% (n=37,192) had no diabetes, 17.6% (n=7,952) were type 2 diabetic (T2DM) and 0.3% (n=129) had type 1 diabetes (T1D). All patients completed questionnaires for demographics, hypoglycemia fear survey (HFS II), hypoglycemia unawareness (Clarke's method) and assessment of comorbidities. A1c was measured, and blinded CGM was performed over a 2-week period.

Conclusion: In nondiabetics there was higher mortality at a lower CVG as compared to the diabetics. In diabetics the increased mortality was observed at slightly higher CVG. In patients admitted to critical care units, increased fluctuation in glucose during their ICU admission is an independent predictor of mortality and additional caution should be taken to avoid wide fluctuations.

---

**403-P**

**Postprandial Insulin Initiation—Evaluation of Adverse Outcomes in Older Veterans**

CHIN-LIN TSENG, ORYSYA SOROKA, LEONARD POGACH, Boston, MA

We assessed one-year adverse outcomes (emergency department visits for hypoglycemia, death, and potential overtreatment (A1c <6.5%) post prandial initiation in veterans >= 65 years receiving only basal insulin in 2009-2011 and dually enrolled in Veterans Health Administration and Medicare using linked data. Rates were compared by race (blacks, whites, others) and comorbidity categories (advanced diabetes complications [Ego], diminished life expectancy [LL], major neurological disorders/dementia/cognitive impairment/major depression/substance abuse [M]) and cardio vascular conditions (C). Of the 4,465 studied patients, 457 (13%) died or incurred hypoglycemia-ED of the 200 (58%) that incurred hypoglycemia-ED, 16%, 24%, and 23% had the event in 1, 2, and 4-6 months, respectively; of the 271 (78%) deaths, 88%, 17%, and 15% occurred in the same time intervals. Of the 2,789 (80%) patients having some A1c values within a year post-prandial, 10% had an A1c <6.5%. Compared to whites (n=2,708; 78%), blacks (33%; 10%) had a higher hypoglycemia-ED rate (8.0% vs. 5.6%, p=0.08) and a comparable death rate (8.5% vs. 8.4%, p=0.89). Both races had similar rates of having an A1c <6.5% (11.6% vs. 13.1%, p=0.48). Most (88%) patients had at least one of the studied comorbidity categories; the prevalence order was: C (69%), D (39%), M (21%), and L (16%). Patients with M (21%) had higher rates in adverse outcomes than those with only C (28%) and those without any studied comorbidities (15%): for HYPO-ED, the rates were 6.3%, 5.9%, and 5.4% (p=0.76); for death, 12.6%, 5.8%, and 2.3% (p<0.001); for having an A1c <6.5%, 14.5%, 11.8%, and 10.2% (p=0.11). Among basal insulin users started on prandial, we found that within a year after prandial initiation, HYPO-ED rate was 1.4 fold greater in blacks than whites, patients with mental/cognitive/neurological diseases had higher rates in HYPO-ED and death, and at least one in ten had an A1c <6.5%. Prandial insulin should be used cautiously in older adults with complex comorbidities.

Supported By: U.S. Department of Veterans Affairs (IIR 14-082)

---

**404-P**

**Intensive Hypoglycemia Avoidance and Improved Awareness of Hypoglycemia Associated with Partial Recovery Activation Lost in Hypoglycemia Unaware Patients with Type 1 Diabetes**

PRATIK CHOUDHARY, MUNACHIU NWOKO, OWEN D’OILY, STEPHANIE A. AMIEL, FERNANDO O. ZELAYA, London, United Kingdom

Aim: The brain senses hypoglycemia and governs symptomatic, hormonal and behavioral responses to it. This study aimed to understand the differences in regional brain responses to experimental hypoglycemia between adults with type 1 diabetes (T1D) with intact hypoglycemia awareness (HA) and impaired awareness of hypoglycemia (IAH) and evaluate the impact of intensive hypoglycemia avoidance on these responses.

Methods: We performed ASL fMRI scans to measure global and regional cerebral blood flow (CBF and rCBF) and measured symptomatic and hormonal responses to experimental hypoglycemia (47 mg/dl) in 15 HA T1D subjects and 22 subjects with IAH matched for age, HbA1c and duration of diabetes. Those with IAH underwent a hypoglycemia avoidance program including education, frequent contact and additional technology where required, including sensor augmented pump therapy with predictive low glucose suspension before being restudied with ASL fMRI at hypoglycemia.

Results: Baseline scans: Global CBF increased in response to hypoglycemia in HA and IAH [HA 6.3% p=0.01; IAH 8.0%, p=0.03; HA vs. IAH p=NS]. There was greater increase in CBF in thalamus, prefrontal cortex and orbitofrontal cortex in HA vs. IAH and greater reduction in CBF in the hippocampus. Repeat scans: The hypoglycemia avoidance program improved subjective awareness [Gold score b +1 vs. c +2; 1.9; p=0.001] in the 12 completers. Compared to baseline scans, there was a trend to greater increase in CBF in the anterior cingulate cortex in response to hypoglycemia [p=0.058], but no changes in the thalamus, prefrontal or orbitofrontal cortices.

Conclusion: Intensive education and support can improve hypoglycemia awareness with some restoration of activation in the anterior cingulate cortex, but frontal changes are not restored suggesting cognitive responses to hypoglycemia may not be changed by these interventions.

Supported By: Diabetes UK

---

**405-P**

**Risk of Hypoglycemia in Aging Population with Insulin-Requiring Diabetes**

MEDIHA MUNSHI, CHRISTINE SYLVE, ASTRID ATAOKAV-CASTILLO, JORDAN GREENBERG, TORI GREALVES, SAM P. CARL, ELENA TOSCHI, Boston, MA

Background: The impact of aging on insulin-dependent diabetes is not well studied.

Methods: We evaluated insulin-dependent older adults (age >65 years) with type 1 (T1D) and type 2 diabetes (T2D). All patients completed questionnaires for demographics, hypoglycemia fear survey (HFS III), hypoglycemia unawareness (Clarke’s method) and assessment of comorbidities. A1c was measured, and blinded CGM was performed over 2-week period.

Results: We evaluated 32 insulin-dependent older adults: 23 had T1D (age 70±4 years, A1C 8%) and 9 had T2D (age 80±9 years, A1C 8.9%). All with T1D were either on insulin pump or on a 4-in-1 insulin injections/day compared to 55% of patients with T2D. Clinically significant hypoglycemia (glucose <55 mg/dl for ≥ 20 mins/episode) was observed in 91% of patients with T1D (21 of 23), compared with 22% with T2D (2 of 9). Noncutaneous hypoglycemic episodes (10 pm-8 am) were observed in 15 out of 23 (65%) T1D patients, compared to 1 out of 9 (11%) with T2D. Older adults with T1D had greater fear of hypoglycemia as shown by HFS II score of 34 compared to 15 in T2D. However, hypoglycemia unawareness was similar in the two groups (8 of 23 (39%) with T1D, and 3 of 9 (33%) with T2D. Age-associated comorbidities in T1D and T2D older adults included Cognitive impairment (66% vs. 100%), depression (27% vs. 43%), recent falls within 6-months (24% vs. 43%), vision impairment (27% vs. 43%), and hearing impairment (38% vs. 50%) respectively.

Conclusions: Insulin-dependent older adults with T1D have a higher risk of total and nocturnal hypoglycemia compared to older adults with T2D. Associated multiple age-related comorbidities put them at higher risk of poor outcomes.
Inhibition of Drp1-Mediated Mitochondrial Fission Protects Diabetic Heart against Ischemia-Reperfusion Injury
MIN JIN DING, JIAHAO FENG, ZEYANG LI, FENG FU, Kuan China
We hypothesized that inhibition of Drp1-mediated mitochondrial fission may be effective to reduce MI/R injury in diabetic hearts. High-fat diet and streptozotocin-induced diabetic mice were subjected to MI/R or sham operation. Mdivi-1 (1.2 mg/kg), a small molecule inhibitor of Drp1 or vehicle was administered 15 min before the onset of reperfusion. Outcome measures included mitochondrial morphology, mitochondrial function, myocardial injury, cardiac function and oxidative stress. Mitochondrial fission was significantly increased following MI/R as evidenced by enhanced translocation of Drp1 to mitochondria and decreased mitochondrial size. Delivery of Mdivi-1 into diabetic mice markedly inhibited Drp1 translocation to the mitochondria and reduced mitochondrial fission following MI/R. Inhibition of Drp1-mediated mitochondrial fission increased complex I/Ill/IV activity and ATP content and improved cardiac function following MI/R (n = 8, P < 0.01). Moreover, inhibition of Drp1 reduced myocardial infarct size (28.7 ± 4.2% vs. 45.3 ± 4.7% n = 8, P < 0.01) and serum cardiac troponin and lactate dehydrogenase activities. These cardioprotective effects were associated with decreased cardiomyocyte apoptosis and malondialdehyde production and increased activities of antioxidant enzyme manganese superoxide dismutase (n = 8, P < 0.01). These data suggest that Drp1-mediated mitochondrial fission may be a potential novel therapeutic target for diabetic cardiac complications.

Supported By: National Natural Science Foundation of China (81600235, 81670354)

A Risk Prediction Model for Heart Failure Hospitalization among Patients with Type 2 Diabetes
BRENT WILLIAMS, PRANAV GANDHI, Danville, PA, Ridgefield, CT
Type 2 diabetes mellitus (T2DM) is strongly associated with future cardiovascular (CV) events, including heart failure (HF) and its sequelae such as hospitalization (HFH) and death. Identifying T2DM patients at highest risk of HFH may be clinically valuable so therapeutic regimens can be optimized. Accordingly, this study aimed to develop and validate a risk prediction model for HFH among patients with T2DM. This electronic medical record (EMR)-based, retrospective cohort study included patients with new or preexisting diagnoses of T2DM receiving health care services longitudinally through the Geisinger Health System. Study patients were assigned an index date at an office visit at least two years following their first EMR-documented encounter between 1/1/03 and 11/1/15. Candidate predictors of HFH were defined according to EMR documentation in the 2-year period prior to the index date from demographics, vital signs, medical history including diagnoses and procedures, CV-related symptoms, and laboratory tests. Cox proportional hazards regression with stepwise variable selection identified the strongest predictors of HFH. Internal validation was performed by randomly splitting the sample 1:1. Among 71,385 T2DM patients meeting study criteria, median (IQR) age of patients at the index date was 62 (52, 72) years and 49% were male. Over a mean (SD) follow-up of 5.8 (4.2) years, 2903 (3.8%) HFH occurred, and estimated HFH incidence rates at 1, 3, and 5 years after the index date were 0.5%, 1.8%, and 3.0%. The development set model containing the 15 strongest HFH predictors had a c-statistic of 0.833, and the validation set c-statistic was 0.824. The five strongest predictors were age, a history of HF, coronary artery disease, blood urea nitrogen, and HbA1c. The patients with 10% highest risk based on the model had ≥2.0% annual risk of HFH. This proposed model for HFH among T2DM demonstrated strong predictive capability and may be valuable in guiding therapeutic decision making.

Supported By: Boehringer Ingelheim

Incidence of Hypoglycemia Events in a Large, Real-World Diabetes Population
JENNIFER BOLLYKY, WEI LU, JENNIFER SCHNEIDER, Mountain View, CA
Background: It is difficult to accurately determine the frequency of hypoglycemic events in a clinical setting. Remotely captured glucose data from connected meters offers an opportunity to understand real-world treatment effects outside of a clinical trial setting. The Livongo for Diabetes Program provides over 50,000 commercially-insured people with diabetes a cellular-enabled, two-way messaging device that measures and records blood glucose. Free, unlimited blood glucose test strips are also provided.
Methods: We obtained blood glucose (BG) values directly from 35,436 individuals who had been using Livongo connected meters over 3 months. Frequency of BG checking, hypoglycemia event rates (BG<70 mg/dL) and clinically significant hypoglycemia event rates (BG<54 mg/dL) were characterized by age, gender, race, diabetes type, estimated HbA1c and medication use.
Results: The mean percentage of total BG checks <70 mg/dL and <54 mg/dL by medication use and diabetes type are reported in Table below. Conclusions: In a heterogeneous population with type 1 and type 2 diabetes we captured many hypoglycemic episodes, the frequency of which was associated with medication use and diabetes type. The Livongo platform provides an opportunity to understand real-world treatment effects outside of a clinical trial setting.

<table>
<thead>
<tr>
<th>No Meds (N=3181)</th>
<th>Oral Meds Only (N=19,135)</th>
<th>Insulin Once Daily (N=5,315)</th>
<th>Insulin &gt; Once Daily</th>
<th>T2D (N=5,315)</th>
<th>Insulin &gt; Once Daily</th>
<th>T1D (N=204)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>BG&lt;70 mg/dL</td>
<td>1.08%</td>
<td>3.95%</td>
<td>1.14%</td>
<td>3.95%</td>
<td>1.14%</td>
<td>3.95%</td>
</tr>
<tr>
<td>BG&lt;54 mg/dL</td>
<td>0.30%</td>
<td>2.23%</td>
<td>0.25%</td>
<td>2.23%</td>
<td>0.25%</td>
<td>2.23%</td>
</tr>
</tbody>
</table>
Complications—Macrovacular—Atherosclerotic Cardiovascular Disease and Human Diabetes

410-P
Pro-B-Type Natriuretic Peptide Strongly Predicts Future Cardiovascular Events in Cardiovascular Patients with Type 2 Diabetes as Well as in Those Without Type 2 Diabetes

Christoph H. Saely, Alexander Vonbank, Christine Henzle, Danela Zanolin, Barbara Larcher, Arthur Mader, Andreas Lehner, Axel Muendlein, Heinz Drexl

Background: The Exenatide Study of Cardiovascular Event Lowering (EXSCEL) was recently published. Thus, we here present a mixed treatment comparison meta-analysis of MTCs of major randomized clinical trials to determine Glucagon-like peptide 1 (GLP-1) receptor agonists’ effects on CV outcomes in patients with T2DM.

Methods: A comprehensive, systematic review was conducted using Embase and MEDLINE databases. Studies were included in the MTC meta-analysis if they were (1) RCTs and (2) evaluated the effects of one of the GLP-1 agonists vs. placebo on CV outcomes as their primary endpoint. The primary outcomes were CV death, nonfatal MI, and nonfatal stroke. Heterogeneity for HF was evaluated as a secondary endpoint.

Results: A total of 202 publications were identified and reviewed, of which 198 were excluded based on study design or relevance to the research question. A total of 4 trials, including 33,457 patients, met the inclusion criteria. Three trials with 33,413 patients were included in the MTC meta-analysis. In conclusion, chronic diabetes in Yucatan miniature swine manifests with progressive effects on heart rate, PR interval, and QRS duration. This indicates that the diabetic minipig could provide a good model to test preventive approaches for progressive cardiac therapies in diabetes, using electrocardiography segments as markers of early heart damage.

Effects of Glucose and Blood Pressure Variability on Oxidative Stress in Type 2 Diabetes with Hypertension

Aims: This study was performed to evaluate the effects of glucose variability and blood pressure variability (BV) on oxidative stress in type 2 diabetes patients with hypertension.

Methods: Fifty-seven inpatients with type 2 diabetes (studied from May 2015 to August 2017) underwent continuous glucose monitoring (CGM) and ambulatory BP monitoring (ABPM) in a cross-sectional study. The plasma total oxidant capacity against N, N-diethyldithiophenylendiamine was measured as a marker of oxidative stress using the d-ROMs test. The GV, mean glucose level (MGL), mean amplitude of glycemic excursions (MAGE), and standard deviation of blood pressure (SDBP) during the systole (S) and diastole (D) were measured by ABPM over day (day), nighttime (night), and 24-hour (24) periods. In univariate analysis, MAGE (β=0.446, p<0.001), night DBP (β=0.132, p=0.014), and eGFR (n=0.287, p=0.030) were significantly correlated with the d-ROMs. In the stepwise multiple regression analysis, MAGE (β=0.334, t=3.075, p=0.003), night DBPS (β=0.230, t=2.034, p=0.047), eGFR (β=0.254, t=2.137, p=0.037), and smoking (β=0.315, t=2.873, p=0.006) were identified as independent factors contributing to the d-ROMs (multiple R²=0.363).

Conclusions: Daily glucose variability and nighttime systolic blood pressure variability are associated with oxidative stress in type 2 diabetes with hypertension.

412-P
The Effect of Bariatric Surgery on Neprilysin and Vasoactive Factors

Pareesh Dandona, Hussam Ghanim, Scott Monte, Kelly Green, Joseph A. Caruana, Williamsburg, NY; Buffalo, NY; Orchard Park, NY

Objective: Since morbid obesity is associated with congestive cardiac failure and hypertension, and gastric bypass surgery is followed by a reduction in blood pressure and a reduction in the risk of congestive cardiac failure, we hypothesized that weight loss following bariatric surgery in morbidly obese patients is associated with a decrease in plasma concentrations of neprilysin, mediators of renin-angiotensin system, catecholamines and endothelin-1 with an increase in the concentrations of vasodilators.

Methods: Fasting blood samples were obtained from fourteen patients with morbid obesity and diabetes prior to and 6 months after Roux-en-Y gastric bypass (RYGB) surgery. Plasma and serum were separated for the measurement of neprilysin; vasconstrictors, angiotensinogen, renin, angiotensin II, endothelin-1, epinephrine and norepinephrine; and vasodilators, ANP, BNP, cGMP, and cAMP. The mRNA expression of angiotensin converting enzyme (ACE) and adenylyl and guanylyl cyclases in circulating mononuclear cells (MNC) was also measured.

Results: Six months after RYGB, BMI fell from 52.1±4.8 to 40.4±4.0 kg/m² and there were significant improvements in the HbA1c. Plasma concentrations of neprilysin, angiotensinogen, angiotensin II, renin and endothelin-1 fell significantly by 27±16%, 22±10%, 22±8%, 35±13% and 17±6% (p<0.05 for all respectively, while ANP concentrations increased significantly by 24±13% at 6 month following surgery. There was no significant change in aldosterone, BNP, cAMP or cGMP concentrations and ACE mRNA expression.

Conclusion: RYGB suppressed neprilysin concentrations, which may contribute to the observed increase in plasma ANP concentrations. In addition, RYGB resulted in a reduction in plasma angiotensinogen, angiotensin II, renin and endothelin-1 concentrations. These changes may contribute to the reduction in the risk of congestive cardiac failure and blood pressure after RYGB.

413-P
Electrophysiological Assessment of Cardiac Complication in Chronic Diabetic Minipigs

Alain Strickler-Krönig, Jason Liu, Guy Boulevard, Alkmaar, NL

Abundant evidence shows that patients with type 1 diabetes are at high risk for several cardiovascular disorders. Our objective was to assess cardiac electrophysiological changes linked to chronic insulin-dependent diabetes in the Yucatan miniature swine (total N = 22). Diabetic animals were divided into different groups based on duration of diabetes (Group 1: normal, 2–3.4 years; Group 2: 3–4.5 years; Group 3: 4.5–5.5 years). Cardiac electrophysiological parameters were acquired in conscious diabetic and normal control animals using an standard lead II configuration. Routine measurements of electrocardiograms, including HR (bpm), PR, RR, QRS, QT and QTc, were done (all in msec). A heart rate correction for the QT interval (QTc) was calculated using the Fridericia method (QTc=QT/[cubed root of RRI]). Mean heart rate was decreased for the diabetic Groups 2, 4, and 5 compared to the mean heart rate for normal animals (52, 54 vs. 75 bpm, respectively). The mean PR interval was increased in all diabetic animals compared to normal animals and the effect increase with the duration of diabetes (132 vs. 138, 140, 152 and 172 msec for Groups 1, 2, 3, 4 and 5, respectively). There were no pronounced QTc abnormalities in this study when comparing diabetic to the normal animals although one animal in Group 3 did have a QTc prolongation of 43 msec. In addition, one animal in Group 5 had a prolonged PR segment (224 msec) associated with frequent ventricular escape complexes.

In conclusion, chronic diabetes in Yucatan miniature swine manifests with progressive effects on heart rate, PR interval, and QRS duration. This indicates that the diabetic minipig could provide a good model to test preventive approaches for progressive cardiac therapies in diabetes, using electrocardiography segments as markers of early heart damage.
eligibility criteria and were retained for analysis. The pairwise meta-analysis showed a 13% reduction in death from cardiovascular causes in patients who received GLP-1 agonists vs. those who received placebo (RR 0.87, 95% CI: 0.78-0.96, I²=0%, P=0.592). The NMA showed no differences among all the interventions, with iraglutide the preferred agent (53%) followed by semaglutide (19%). The pairwise meta-analysis showed no significant reduction in non-fatal MI events between the two groups (RR 0.95, 95% CI: 0.88-1.04, I²=19.5%, P=0.293). Like the pairwise meta-analysis, the NMA results showed no reduction in non-fatal MI events with semaglutide as the preferred agent (86%), followed by iraglutide (14%).

Conclusion: GLP-1 therapy was associated with a significant reduction in CV death. However, GLP-1 agonists seem to have a safety profile comparable to placebo in terms of reducing non-fatal MI, non-fatal stroke events, and rates of HF hospitalization.

PCSK9 has been proposed to play a crucial role in the pathogenesis of atheriosclerotic lesion in addition to hepatocytes. PCSK9 constitutes the atheriosclerotic lesion in addition to hepatocytes. PCSK9 promotes foam cell formation by suppressing the excretion of cholesterol from macrophages. Recently, statin is demonstrated to promote PCSK9 production. PCSK9 has been proposed to play a crucial role in the pathogenesis of IST resistance. The present study was performed to establish a novel therapeutic approach to IST resistant vulnerable plaque of coronary artery in diabetic patients.

Methods: The present study included 106 T2DM patients with non-FHC asymptomatic CAD who developed vulnerable plaques in coronary artery despite IST over 1 year. CTTA by use of 320-slice CT was applied to evaluate vulnerable plaques in coronary artery. During the administration of anti-PCSK9 antibody, changes in serum lipids and CT value of vulnerable coronary plaques were determined.

Results: After the administration of anti-PCSK9 antibody, 72% decrease in serum LDL-C was observed. Also, improvement of vulnerable coronary plaque e.g., rise in the CT value of plaque (from 45.2 ± 12.0 HU to 107.5 ± 42.3 HU, p<0.0001) was observed in 6 months after administration of the drug.

Conclusion: A significant improvement in vulnerable coronary plaques was observed in the patients with asymptomatic CAD who are resistant to IST after 6 months administration of anti-PCSK9 antibody. An analysis of the plaque quality by CCTA is useful method for the evaluation of the effect of the drug on vulnerable coronary plaques.

Diabetes Mellitus and High Triglycerides Are Significant Predictors of Major Cardiovascular Events and Increased Health Care Costs and Resource Utilization—A Real-World Analysis of High-Risk Statin-Treated Patients

Peter P. Toth, Craig B. Grunowitz, Michael Hull, Sephy Philip, Sterling I, Bedminster, NJ, Eden-Prairie, MN

Background: Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality in patients with diabetes. We investigated real-world impact of high triglycerides (TG) and diabetes on cardiovascular (CV) outcomes and costs.

Methods: This retrospective administrative claims multivariate analysis (controlled for patient characteristics and comorbidities) of the Optum Research Database included patients aged ≥45 years with diabetes and/or ASCVD who had a statin prescription filled in 2010, had continuous medical/pharmacy coverage, and were followed for ≥6 months up to March 2016. Patients with TG <150 mg/dL (n=12,411) and a comparator cohort with TG >150 mg/dL and high-density lipoprotein cholesterol (HDL-C) <40 mg/dL (n=52,506) were included.

Results: Multivariate analyses showed a 39% higher rate of occurrence of composite major CV events per unit time in the high-TG vs. comparator cohort (hazard ratio [HR] 1.349, 95% CI 1.225-1.465, P<0.001). Diabetes was found to be a significant predictor of CV events, costs, and risk of inpatient hospital stay (Table).

Conclusions: In statin-treated patients with high CV risk, high TG and diabetes were found to be significant predictors of worse CV and health economic outcomes in a real-world setting.

415-P

A Novel Therapeutic Approach to Intensive Statin Therapy–Resistant Vulnerable Plaque of Coronary Artery in Diabetic Patients by Use of Anti-PCSK9 Antibody and Coronary CT Angiography (CCTA)

Aizan Hirai, Koji Fujimura, Saiya Kondo, Takanori Sakai, Shin Kijima, Hisanori Tai, Ichiro Ohnuki, Kazuya Murata, Atsushi Shirakami, Kazuhiro Ikuizaki, Takahiro Kageyama, Ichihana, Chiba, Japan, Usuki, Japan, Yawatahama, Japan, Odake, Japan, Yurinohyo, Japan, Saitama, Japan, Ise, Japan, Tokushima, Japan

Purpose: Coronary plaque progression despite very low levels of LDL-C has been reported in the patients with coronary artery disease (CAD) who received intensive statin therapy (IST). CCTA has been applied to detect vulnerable coronary plaques having low attenuation of CT value. The best characterized function of PCSK9 is the binding to hepatic LDL receptors, leading to the degradation. PCSK9 is produced also in vascular smooth muscle cells contributing the atherosclerotic lesion in addition to hepatocytes. PCSK9 promotes foam cell formation by suppressing the excretion of cholesterol from macrophages. Recently, statin is demonstrated to promote PCSK9 production. PCSK9 has been proposed to play a crucial role in the pathogenesis of IST resistance. The present study was performed to establish a novel therapeutic approach to IST resistant vulnerable plaque of coronary artery in diabetic patients.

Methods: The present study included 106 T2DM patients with non-FHC asymptomatic CAD who developed vulnerable plaques in coronary artery despite IST over 1 year. CTTA by use of 320-slice CT was applied to evaluate vulnerable plaques in coronary artery. During the administration of anti-PCSK9 antibody, changes in serum lipids and CT value of vulnerable coronary plaques were determined.

Results: After the administration of anti-PCSK9 antibody, 72% decrease in serum LDL-C was observed. Also, improvement of vulnerable coronary plaque e.g., rise in the CT value of plaque (from 45.2 ± 12.0 HU to 107.5 ± 42.3 HU, p<0.0001) was observed in 6 months after administration of the drug.

Conclusion: A significant improvement in vulnerable coronary plaques was observed in the patients with asymptomatic CAD who are resistant to IST after 6 months administration of anti-PCSK9 antibody. An analysis of the plaque quality by CCTA is useful method for the evaluation of the effect of the drug on vulnerable coronary plaques.

416-P

Diabetes Mellitus and High Triglycerides Are Significant Predictors of Major Cardiovascular Events and Increased Health Care Costs and Resource Utilization—A Real-World Analysis of High-Risk Statin-Treated Patients

Peter P. Toth, Craig B. Grunowitz, Michael Hull, Sephy Philip, Sterling II, Bedminster, NJ, Eden-Prairie, MN

Background: Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality in patients with diabetes. We investigated real-world impact of high triglycerides (TG) and diabetes on cardiovascular (CV) outcomes and costs.

Methods: This retrospective administrative claims multivariate analysis (controlled for patient characteristics and comorbidities) of the Optum Research Database included patients aged ≥45 years with diabetes and/or ASCVD who had a statin prescription filled in 2010, had continuous medical/pharmacy coverage, and were followed for ≥6 months up to March 2016. Patients with TG ≥200-499 mg/dL (n=3,411) and a comparator cohort with TG <150 mg/dL and high-density lipoprotein cholesterol (HDL-C) <40 mg/dL (n=52,506) were included.

Results: Multivariate analyses showed a 39% higher rate of occurrence of composite major CV events per unit time in the high-TG vs. comparator cohort (hazard ratio [HR] 1.349, 95% CI 1.225-1.465, P<0.001). Diabetes was found to be a significant predictor of CV events, costs, and risk of inpatient hospital stay (Table).

Conclusions: In statin-treated patients with high CV risk, high TG and diabetes were found to be significant predictors of worse CV and health economic outcomes in a real-world setting.
ACUTE AND CHRONIC

P<0.001) and CRP (ear relationship with HbA1c (pared to Chinese (-0.1±1.2) and Malays (-0.1±1.0); p=0.01. OXY exhibited a lin-
were assessed by student’s t test and Kruskal Wallis test respectively.
using multiple regression analysis. Associations with gender and ethnicity
The total oxidative index (OXY) was calculated as the difference between
oxidative stress in type 2 diabetes mellitus (T2DM).

TOTAL OXIDATIVE INDEX IS ASSOCIATED WITH GLYCEATED HEMOGLOBIN, LOW-GLYCO AL INFLAMMATION, AND NON-HDL CHOLESTEROL IN TYPE 2 DIABETES
RINKOOS DALAN, LIUH UNG GDH, XIN TANG, DANIEL E.K. CHEW, BERNHARD BOEHM, SINGAPORE, SINGAPORE

OBJECTIVES: To study associations of established cardiovascular risk fac-
ors, inflammation and cardiot artery intima-media thickness (CIMT) with
oxidative stress in type 2 diabetes mellitus (T2DM).

METHODS: We recruited 343 T2DM subjects from the three main ethnic
groups in Singapore (Chinese: 196, Indians: 106, Malays: 41; Age: 54.7±10.4 years;
Males: 46%). Measurements: Demographics, BMI, blood pressure, HBAlc, glucose and lipids; CIMT and C-reactive protein (hsCRP). Derivatives of reactive oxygen metabolites (dROMS) and total anti-oxidant status (TAC) was estimated by the automated chemical analysis method (Diacon, Italy).
The total oxidative index (DXY) was calculated as the difference between
standardised dROMS and TAC values. The relationship between DXY, dROMS and
TAC as dependent variable and age, gender, ethnicity, BMI, blood pres-
sure, HBAlc, fasting lipids, log CRP and CIMT as co-variables was assessed using
multiple regression analysis. Associations with gender and ethnicity
were assessed by student’s t test and Kruskal Wallis test respectively.

RESULTS: The mean DXY was higher in the females (2.0±1.3) compared to
the males (0.2±1.0; p<0.001) and highest in the Indians (0.2±1.2) when com-
pared to Chinese (0.1±1.2) and Malays (0.1±1.0; p<0.01). DXY exhibited a lin-
ear relationship with HBAlc (p<0.001), Non-HDL cholesterol (p<0.001), CRP (p<0.001) and TAC associated inversely with non-
HDL-cholesterol (p<0.001). No association with CIMT was seen.

CONCLUSIONS: In T2DM, total oxidative stress is a function of HBAlc,
non-HDL-Cholesterol and low-grade inflammation. HBAlc and inflamma-
tion increase reactive oxygen metabolites, whereas non-HDL cholesterol
decreases the anti-oxidant potential. The mechanisms of oxidative stress
generation, in particular in various ethnic groups, needs to be studied
further.

Supported By: National Medical Research Council of Singapore

PREVALENCE OF PREEXISTING DYSGLYCEMIA AMONG INPATIENTS WITH ACUTE CORONARY SYNDROME AND ASSOCIATIONS WITH OUTCOMES
DINESH MAHENDRAN, GARRY HAMILTON, JEREMY WEISS, JEREMY LEW, KAY-
LYN KOH, ELI F. EKINCI, CANNEGGIE, AUSTRALIA, MELBOURNE, AUSTRALIA, HEIDELBERG, AUSTRALIA

OBJECTIVE: We aimed to determine the prevalence of preexisting dysgly-
cemia in inpatients admitted with acute coronary syndrome (ACS), their
characteristics and, association with acute and 12-month clinical outcomes.
Research Design and Methods: In this prospective observational cohort
study, admission HBAlc testing was undertaken on consecutive inpatients
aged ≥54 years admitted with ACS. Patients were categorised into those with
diabetes (prior diagnosis or HBAlc ≥ 6.5%, ≥48mmol/mol), prediabetes (HBAlc
7.5-8.4%, 39-46mmol/mol) and no diabetes (HBAlc<5.6%, <38mmol/mol).
Results: Between July 2013 and July 2015, 847 consecutive inpatients
aged ≥54 years were admitted with ACS. 313 (37%) inpatients had diabetes,
312(37%) had prediabetes and 222(25%) had no diabetes. After adjusting
for age, sex, smoking status and previous myocardial infarction, diabetes,
as opposed to no diabetes, was associated with higher odds of Acute Pulmo-

ary Oedema (APO) (OR 2.60, P<0.01), longer length of stay (LOS) (IRR
1.18, P=0.02) and, higher odds of 12-month ACS recurrence (IRR 1.86, P<0.05).
Prediabetes was not a statistically significant marker of adverse clinical out-
comes. However, analysed as a continuous variable, every 1% (11mmol/
mo1) increase in HBAlc was associated with increased odds of APO (OR 1.28,
P=0.02) and, longer LOS (IRR 1.05, P=0.03).

Conclusions: In our study, three-quarters of all inpatients aged ≥54 years
admitted with ACS had preexisting dysglycemia. Inpatients with diabetes
had increased odds of APO, longer LOS and higher 12-month ACS recurrence.
Higher HBAlc, was associated with increased odds of APO and longer LOS.
Randomised studies with cardioprotective anti-hyperglycaemic agents
are necessary in determining if improving dysglycemia in ACS patients
improves clinical outcomes.

NEXT GENERATION OF SPONTANEOUS DIABETIC MODEL OF ZDSD RATS WITH INACT LevEPTIN SIGNALING DEPIVING CARDIA Dysfunction AND COMPO-
ISED Cardiac Reserve
GAO SUN, GUODONG ZHANG, YIXIN WANG, Taicang, China

INTRODUCTION: Cardiomyopathy is the leading cause of morbidity and mor-
tality among all complications of type 2 diabetic (T2D) and obese patients.
Diabetic cardiomyopathy (DC) is characterized by an initial cardiac hypertro-
phy followed by thinning of the cardiac walls with declines in both systolic
and diastolic functions, which ultimately leads to heart failure. No rodent
models fully captured phenotypes of DC. The ZDSD rat, a new generation of
T2D rat model with intact leptin signalling features with slow onset of dia-
betes and obesity, which closely mimics the development of the disease in
patients. Here we sought to evaluate the cardiac function during the devel-
ompent of metabolic syndromes in ZDSD rats.

Methods: 12 male ZDSD rats and age-matched SD controls were moni-
tored for blood pressure, glucose, and cardiac function using echocardiogra-
phy. Animals were also challenged with 1 mg/kg dobutamine for the assess-
ment of cardiac reserve.

Results: ZDSD rats developed hypertension from age of 18 weeks. Their
left ventricular (LV) functions were compromised along with changes in car-
diac morphology. At resting state, ZDSD rats showed thinning of LV wall,
or increase in LV end-diastolic volume. At 34 weeks of age, both ejection fraction (EF) and tranmural E/A ratio declined. Upon treatment with dobutamine for 5 minutes, SD rats
reached almost 98% EF, while the values of ZDSD were 91% at 30 and 34
weeks old, suggesting the loss of LV contractility the animals.

Conclusion: ZDSD rats which carry multiple dysmetabolic phenotypes
are spontaneously hypertensive with reduction in LV function, a metabolic
reserve which resembles ultrasonic symptoms of diabetic cardiomyopathy
patients. Therefore, ZDSD rats may serve as a suitable preclinical model to
study potential therapeutic approaches to treat cardiomyopathy with pres-
ence of metabolic syndromes.
Plasma Omentin Levels Are Associated with Atherosclerosis in Patients with Type 2 Diabetes

MASAMI HATAMORI, TOMOAKI MORIOKA, MARIKO SENDA, MARIKO ASADA, YOSHINORI KAKUTANI, YUKI YAMAZAKI, KOKE MOTODA, KATSUHIRO MORI, SHINYA FUKUMOTO, ATSUSHI SHIOJI, MASANORI EMOTO, MASAKI INABA, Osaka, Japan

Omentin is an adipokine predominantly expressed in visceral adipose tissue and has insulin-sensitizing and vasculoprotective effects, like adiponectin, in rodents. Previous studies indicated an association of plasma omentin levels with atherosclerosis, vascular endothelial function, and coronary artery disease in nondiabetic individuals. In this study, we investigated the association between plasma omentin levels and atherosclerosis in patients with type 2 diabetes. We included 416 patients with type 2 diabetes in this study. Fasting plasma omentin levels and total adiponectin levels were measured by ELISA, and the mean intima media thickness (IMT) of the common carotid artery was measured by ultrasonography. The medians of plasma omentin level, adiponectin level, and IMT were 572 ng/mL, 6.1 µg/mL, and 0.76 mm, respectively. Eighty seven (21%) subjects had cardiovascular diseases (CVDs), including coronary artery disease, cerebrovascular disease, or peripheral artery disease, which were confirmed by medical records.

Plasma omentin levels were positively correlated with adiponectin and HDL cholesterol, and negatively correlated with BMI, IRI, HOMA-R, triglycerides, and eGFR. Multivariate analysis showed that plasma omentin levels were not significantly associated with IMT after adjustment for adiponectin and traditional CVD risk factors. However, subgroup analysis revealed that plasma omentin level was an independent determinant of IMT (β = 0.138, p = 0.015) in subjects without CVDs, but not in those with CVDs. Interaction analysis indicated a potential effect modification by the presence of CVDs on the association of plasma omentin levels with IMT.

In conclusion, plasma omentin levels are associated with atherosclerosis, independently of adiponectin and traditional CVD risk factors, in patients with type 2 diabetes without CVDs. This study indicates a protective role of omentin in atherosclerosis among patients with type 2 diabetes without CVDs.

Plasma Omentin Levels Are Associated with Vascular Endothelial Function in Patients with Type 2 Diabetes and Cardiovascular Diseases

MARIKO SENDA, TOMOAKI MORIOKA, MARIKO ASADA, YOSHINORI KAKUTANI, YUKI YAMAZAKI, KOKU MOTODA, KATSUHIRO MORI, SHINYA FUKUMOTO, ATSUSHI SHIOJI, TETSUO SHOJI, MASANORI EMOTO, MASAKI INABA, Osaka, Japan

Omentin is an adipokine predominantly expressed in visceral adipose tissue and has insulin-sensitizing and vasculoprotective effects, like adiponectin, in rodents. Previous studies indicated associations of plasma omentin levels with atherosclerosis, vascular endothelial function, and coronary artery disease in nondiabetic individuals. In this study, we investigated the association between plasma omentin levels and vascular endothelial function in patients with type 2 diabetes. We included 428 patients with type 2 diabetes in this study. Fasting plasma omentin levels and total adiponectin levels were measured by ELISA, and the endothelium-dependent, flow-mediated dilatation (FMD) of the brachial artery was measured by ultrasonography. The medians of plasma omentin level, adiponectin level, and FMD were 572 ng/mL, 6.1 µg/mL, and 5.7%, respectively. Ninety one (21%) subjects had cardiovascular diseases (CVDs) which were confirmed by medical records. Plasma omentin levels were positively correlated with adiponectin and HDL cholesterol, and negatively correlated with BMI, IRI, HOMA-R, triglycerides, and eGFR. Multivariate analysis showed that plasma omentin levels were not significantly associated with FMD after adjustment for adiponectin levels and traditional CVD risk factors. However, subgroup analysis revealed that plasma omentin level was an independent determinant of FMD (β = 0.403, p = 0.002) in subjects without CVDs, but not in those with CVDs. Interaction analysis indicated a potential effect modification by the presence of CVDs on the association of plasma omentin levels with FMD.

In conclusion, plasma omentin levels are associated with vascular endothelial function, independently of adiponectin and traditional CVD risk factors, in patients with type 2 diabetes and CVDs. This study indicates a protective role of omentin in vascular endothelial function among patients with type 2 diabetes and CVDs.

Early Vascular Parameters in the Micro- and Macrocirculation in Type 2 Diabetes

ROLAND E. SCHMIDT, DENNIS KANNENKERIL, MARINA V. KARG, AGNES BOEGH, JOANNA M. HARAZNY, SR., CHRISTIAN OTT, Erlangen, Germany

Background: In a large cross-sectional analysis we analyzed various vascular parameters in the renal, retinal and systemic circulation, with the goal to identify which vascular parameter of early organ damage is the earliest that can be clinically detected.

Methods: In 111 patients with type 2 diabetes (T2DM) and 54 subjects without T2DM we assessed urinary albumin creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR), retinal capillary flow (RCF), intercapillary distance (ICD) as parameters of capillary rarefaction, wall-to-lumen ratio (WLR) of the retinal arterioles [all assessed by Scanning Laser Doppler Flowmetry], and central systolic pressure (cSBP) and central pulse pressure (cPP) [measured by pulse wave analysis, Syphymocor].

Results: Compared to subjects without T2DM, patients with type 2 diabetes (duration: mean 63.9 ± 56.4, range 1-271 months) were older (59.8 ± 7.3 vs. 43.4 ± 12.9 years; p < 0.001), more females (33.3% vs. 20.4%, p < 0.001) but 24-hour systolic and diastolic blood pressure did not differ between the two groups (129 ± 11/76 ± 8 vs. 130 ± 11/77 ± 9 mmHg).

Conclusion: These data suggest that at similar blood pressure capillary rarefaction in the retinal circulation (ICD), eGFR in the renal circulation and central pulse pressure (cPP) of large arteries are earlier detectable than vascular remodeling of peripheral micro- (WLR, RCF, UACR) and macrocirculation (cSBP) in patients with T2DM.
Serum FGF-21 is Associated with Future Cardiovascular Events in Patients with Coronary Artery Disease—Results from a Median Follow-Up of 4.8 Years Study

YUQIAN BAO, YUN SHEN, XUELING ZHANG, YITING XU, QIN XIONG, ZHIGANG LU, XIAOLING MA, Shanghai, China

Objectives: To investigate whether the serum fibroblast growth factor (FGF) 21 levels can be used to predict the future development of major adverse cardiovascular events (MACEs).

Methods: 253 patients at baseline received subsequent follow-up, 234 of whom finished the data collection. Independent predictors of MACEs were identified using Cox proportional hazards regression analysis. The prognostic value of FGF-21 levels for MACEs was evaluated by Kaplan-Meier survival analysis.

Results: Of 229 patients finally enrolled in the analysis, 27 of 60 without coronary artery disease (CAD) at baseline experienced a MACE, and 132 of 169 patients with CAD at baseline experienced a MACE. Among patients with CAD at baseline, serum FGF-21 levels were significantly higher in patients with MACEs (P<0.05) than in patients without MACEs. Kaplan-Meier survival analysis showed a significantly lower event-free survival (P=0.001) among patients with a higher serum FGF-21 level than in those with a lower serum FGF-21 level. Further Cox proportional hazards regression analysis, including the traditional risk factors for cardiovascular disease, showed that serum FGF-21 was one of the independent predictors of the occurrence of MACEs.

Conclusions: In patients with CAD at baseline, an elevated serum FGF-21 level was associated with the development of a MACE in the future.

Supported By: Shanghai Jiao Tong University School of Medicine (15ZH4006)

Elevated Fibroblast Growth Factor-21 Protect Endothelial Function in Type 2 Diabetes Patients

YANJUN HUI, YUAN XU, GUANG WANG, Beijing, China

Background: Fibroblast growth factor factor 21 (FGF-21) is a metabolic regulator with multiple effects on improving glucose metabolism and energy utilization. Recent researches pointed that FGF-21 protect endothelial function against high glucose induced cell damage. Our research tried to detect the relationship of FGF-21 and endothelial dysfunction in newly diagnosed type 2 diabetes (T2D) patients.

Methods: Fifty newly diagnosed T2D patients and fifty healthy controls were recruited in the research. Clinical and biological data, FGF-21 were measured. Endothelial function was tested by reactive hyperaemia index (RHI) approved by American Food and Drug Administration.

Results: T2DM patients had higher FGF-21 levels (155.57±85.3 vs. 117.39±69.9ug/l, P<0.05) and more serious endothelial dysfunction (1.73±0.51 vs. 2.05±0.52, P<0.05) than controls. RHI was negatively related with low density lipoprotein cholesterol (LDL-C) (r=-0.322, P<0.05) and positively with FGF-21 (r=0.543, P<0.01). In the multivariate linear analysis, FGF-21 (β=0.551, P<0.01) and LDL-C (β=0.188, P<0.01) were independently predictors of RHI. FGF-21 was the protective factor of endothelial function in the T2D patients.

Conclusions: T2D patients had endothelial dysfunction even in the early period. Elevated FGF-21 might protect endothelial dysfunction.
Pro-Apoptotic and Inflammatory Markers Enhance the Ability of MDA-LDL in Circulating Immune Complex to Predict Acute Myocardial Infarction in the VADT Study

MARIA F. LÓPEZ- VàRELLA, KELLY J. HUNT, RASHI AGARWAL, NATHANIEL L. BAKER, GABRIEL VàRELLA, VAAT INVESTIGATORS, Charleston, SC

There is considerable interest in identifying biomarkers indicative of plaque instability and acute events. Previously we reported that MDA-LDL in circulating immune complex predicted acute myocardial infarction (MI) in the VADT study. Interleukin (IL)-6, Fas Ligand, tissue inhibitor of MMP (TIMP)-1 and monocyte chemotactic protein (MCP)-1 have been identified as potentially clinically relevant biomarkers related to plaque instability. Therefore, our objective was to examine the role of these biomarkers in conjunction with MDA-LDL in circulating immune complex as predictors of acute MI in type 2 diabetes. Biomarker levels were measured in 833 VADT patients, a median of 2.0 years after study entry and participants were subsequently followed a median of 3.7 years. Biomarkers were examined individually and as composite scores created by summing z scores across biomarkers. Hazard ratios (HRs) for acute MI were calculated by Cox proportional hazard models. During follow-up, 5.2% had an MI. After adjustment for conventional risk factors, results of composite biomarkers scores were promising with a hazard ratio for acute MI of 4.65 (95% CI: 1.56, 13.9) comparing the fourth to first quartile of our summary composite score which included MDA-LDL-IC, IL-6, Fas Ligand, TIMP-1 and MCP-1 (Table).

<table>
<thead>
<tr>
<th>Quartile</th>
<th>MDA-LDL-IC</th>
<th>Fas Ligand</th>
<th>TIMP-1</th>
<th>MCP-1</th>
<th>Summary Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Quartile</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Second Quartile</td>
<td>1.49</td>
<td>1.66</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Third Quartile</td>
<td>0.53</td>
<td>0.26</td>
<td>0.26</td>
<td>0.26</td>
<td>0.26</td>
</tr>
<tr>
<td>Fourth Quartile</td>
<td>2.68</td>
<td>2.68</td>
<td>2.68</td>
<td>2.68</td>
<td>2.68</td>
</tr>
</tbody>
</table>

Lower baseline SUMOD also predicted worsening in AA PWV over 3 months (p=0.03). According to SUMOD tertiles, participants in the lower tertile had higher AA PWV vs. the middle and high tertiles (Table). Total and CV mortalities at 12 months after AMI were assessed. Results: A total of 13104 patients with AMI from the registry database were analyzed. 552 patients (4.2%) were destined to in-hospital mortality or hopeless discharge. We classified the remaining patients into control, prediabetes, and diabetes groups according to one of following parameters: prevalent diabetes by past history, diabetes medication during hospitalization, or in the remaining cases with no diabetes history or medication data by hemoglobin A1c level at admission. Patients without any data about above-mentioned parameters were excluded in this study (n=3583), and a total of 8969 AMI patients were available for analysis (control group, n=2375; prediabetes group, n=3231; and diabetes, n=3363). After adjustment for multiple factors, hazard ratios (HRs) (95% CI) for total mortality in prediabetic group vs. control group and diabetic group vs. control group were 1.536 (0.879-2.685, p=0.132) and 1.94 (1.184-3.190), (p<0.01), respectively. However, CV mortality were not different between the three groups. Conclusions: Our results show that that prediabetic state at AMI admission do not increase CV mortality and all-cause mortalities at 1-year after survival discharge, whereas diabetes increase 1-year all-cause mortality.

High Prevalence of Asymptomatic Coronary Artery Disease (CAD) Evaluated by Intravascular Ultrasound (IVUS) in a Norwegian Cohort with Type 2 Diabetes (T2D) as Compared with Asymptomatic Controls without T2D—A Cross-Sectional Study

ANNE F. ØSTFAD, SATISH ARORA, GEIR R. ULIMOEN, KARE I. BIRKELAND, KNUT ENGRESEN, LARS G. GULLESTAD, ODD ERIK JOHANSEN, ROY ORGENSEN, KARIN SCHENDEL, KARE I. BIRKELAND, KNUT LØKEN, OSLO, NORWAY

The prevalence of asymptomatic CAD in T2D is unclear. We investigated the CAD burden using the gold standard IVUS in an asymptomatic T2D-cohort compared to a reference population without T2D. Patients with T2D and ≥ 1 cardiovascular (CV) risk factor (n=56, 21% women, mean age/diabetes duration 65.2±7.1/13.5±6.8 years, HbA1c 7.2±1.1%, systolic BP 136±17 mmHg, LDL-cholesterol 2.5±0.8 mmol/L) underwent invasive coronary angiography with IVUS. Reference population comprised heart transplant donors free from T2D and CAD who had IVUS performed 7-11 weeks post-transplant (n=76). IVUS was described by maximal intimal thickness (MIT), percent atheroma volume (PAV) and normalized total atheroma volume (TAV). All
COMPLICATIONS—MACROVASCULAR—ATHEROSCLEROTIC CARDIOVASCULAR DISEASE AND HUMAN DIABETES

Impact of Human vs. Analog Insulins on Occurrence of Death and Major Cardiovascular Events

EMILY B. SCHROEDER, PATRICK J. O’CONNOR, JULIE SCHMIDTDOEL, KRISTI REYNOLDS, JAY R. DESAI, MICHAEL HO, GABRIELA VAZQUEZ BENITEZ, JEFFREY P. ANDERSON, NOEL PIMENTEL, LINDA M. LOES, ROMAIN NEUGEBAUER, DENVER CQ BLOOMINGTON, NW, OAKLAND CA, PASADENA CA.

Background: This observational study uses rigorous causal inference methods of comparative effectiveness research to emulate a trial evaluating the cardiovascular safety of analog (AI) vs. human insulin (HI).

Methods: On date of first insulin use, 127,600 adults with type 2 diabetes were classified as using: AI with or without HI, or HI only. Separate analyses assessed occurrence of: myocardial infarction (MI), stroke, heart failure hospitalization (HFrEF), cardiovascular (CV) death, or death, censored at disenrollment, start of pregnancy, or 12/31/2013. Marginal structural modeling (MSM) with Inverse Probability Weighting (IPW) was used to compare event free survival in per-protocol analyses in which follow-up data was right-censored for cross-over or interrupted insulin therapy. Adjusted and unadjusted effect estimates were based on two logistic MSM parameterizations for counterfactual hazards. To address potential residual confounding, we conducted four sensitivity analyses with three nested covariate adjustment sets and machine learning for data-adaptive selection of covariates.

Results: Mean follow-up time was 21.8 months. The Table shows hazard ratios (95% CI) of AI vs. HI users for events of interest.

Conclusions: We observed no statistically significant differences in 5 major clinical outcomes between users of AI and HI.

Table.

<table>
<thead>
<tr>
<th>Event</th>
<th>AI vs. HI 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Mortality</td>
<td>1.18 [1.15-1.20]</td>
</tr>
<tr>
<td>CV Mortality</td>
<td>1.09 [1.03-1.16]</td>
</tr>
<tr>
<td>AMI</td>
<td>1.09 [1.02-1.17]</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.08 [1.03-1.14]</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.07 [1.02-1.12]</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.07 [1.02-1.12]</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.07 [1.02-1.12]</td>
</tr>
</tbody>
</table>

Different Augmentation of Left Ventricular Contractility of Mice during Myocardial Infarction following Glipitin and Sulfonylurea Treatment

ELIAS HALJ-YEHIA, SEBASTIAN DIEBOLD, JULIA MOLLERMANN, FLORIAN KAHLES, THOMAS KLEIN, MICHAEL MARK, NIKOLAUS MARK, MICHAEL LEHRKE, Aachen, Germany, Biberach, Germany

DPP-4 inhibitors are a class of antidiabetic drugs which act by augmentation of the GLP-1 system and insulin secretion. Despite similar glucose lowering efficacy within the class, only saxagliptin increased heart failure hospitalization in diabetic patients. This unexpected effect might relate to the metabolism of saxagliptin (saxa). Here, we directly compare linagliptin (lina, 3 mg/kg, p.o.), saxa (10 mg/kg, p.o.), and its metabolite 5-hydroxy-saxagliptin (OH-saxa, 10 mg/kg, p.o.) to the sulfonylurea glimepiride (glim, 2 mg/kg, p.o.) and control during acute myocardial infarction in mice. Millar catheter analysis under dobutamin stress 6h post (permanent) LAD ligation were performed. Drugs were given 3 days prior infarction. Active GLP-1 was significantly increased by Lina (1,69 fold), saxa (1,49 fold) and OH-saxa (2,27 fold) vs. control (each p < 0.05), but not by glim. Despite similar GLP-1 levels, only lina and saxa but not OH-saxa or glim increased left ventricular contractility (Lina: 11.549 ± 795 dp/dt max; p < 0.001; n=9; Saxa: 10.121 ± 260 dp/dt max; p < 0.05; n=12; OH-saxa: 8.201 ± 567 dp/dt max; n=7; Glim: 9.947 ± 813 dp/dt max; n=6) and relative to control: 8.764 ± 284 dp/dt max; n=21). We further isolated mitochondria from non-infarcted myocardial tissue and found for lina 2.89 fold (p < 0.0001; n=3), saxa 1.78 fold (p=0.05; n=8) and OH-saxa 2.2 fold (p < 0.01; n=4) increase in mitochondrial respiration by Clark electrode, but not for glim.

In conclusion, only linagliptin and saxagliptin increased left ventricular contractility and myocardial mitochondrial respiration following LAD ligation; 5-hydroxy-saxagliptin had no effect on contractility despite increasing mitochondrial respiration. Glimepiride had no effect on contractility and mitochondrial function. Metabolism of saxagliptin might be linked to differences found in the DPP-4 class regarding heart failure.
Glycemic Variation and Cardiovascular Risk during the VADT

JIN ZHOU, DAWN SCHWENKE, PETER REAVEN, Tucson AZ, Phoenix A2

There is uncertainty about the importance of visit-to-visit glycemic variability in cardiovascular disease (CVD) complications in type 2 diabetes (T2D) patients. Using the Veteran Affairs Diabetes Trial (VADT), we investigated this relationship, and assessed whether it is influenced by intensive or standard glucose control. During the VADT, fasting glucose and HbA1c were measured every 3 months for up to 84 months in 1791 individuals. Visit-to-visit variability measures included coefficient of variation (CV) and average real variability (ARV). By Cox proportional hazard models, variability measures of fasting glucose showed significant association with CVD even after adjusting for other risk factors, including mean fasting glucose. This relationship was evident in the intensive treatment group but not in the standard group (Figure). Additional adjustment for severe hypoglycemic episodes, did not alter the effect of glucose variability on CVD. Interestingly, HbA1c variability was not associated with CVD after adjusting for multiple baseline risk factors. Our analysis indicates that in the VADT, variability of fasting glucose plays a role in the development of CVD complications beyond the influence of the mean glucose measures. The adverse consequences of glucose variability on CVD appear greatest in those receiving intensive glucose control.

Figure: Hazard ratio (HR) estimates for quintiles of Log (CV)-glucose and ARV-glucose for the primary composite CVD outcome adjusted for ethnicity, baseline HbA1c, baseline HDL and LDL cholesterol, baseline total cholesterol and triglycerides, history of hypertension, diabetes duration, prior CVD event, and the cumulative mean of glucose. Vertical bars are the 95% confidence interval (95% CI) associated with HR estimates. *** indicates estimated HR in the related variability quintile is significantly higher than the HR of lowest variability quintile (quintile 1).

Liraglutide Effects in Insulin-Treated Patients in LEADER

CORNEILUS TACK, STEPHAN JACOB, CYRUS DESOUZA, STEPHEN C. BAIN, MICHAEL A. NAUCK, JOHN PETRIE, NEIL R. POULTER, RICHARD E. PRATLEY, HELEN VANYA BIERING KJAER STEGMANN, INGER K. DAHL-PETERSEN, CHRISTINA V. LARSEN, MICHAEL L. PEDERSEN II, ANDERS ALBRECHTSEN, IDA MOLTE, NIELS GRARUP, TORBEN HANSEN, GENTOFTE, Copenhagen, Denmark, Naun, Greenland.

The objective of this study was to evaluate the association between fast- ing insulin concentration—as a cardiovascular risk factor—and the high density lipoprotein cholesterol level in patients with chronic hepatitis C. The study included 171 patients from Bucharest, to which were followed anthropometric indexes. Biochemical parameters followed were glucose fasting insulin, glycosylated hemoglobin, lipid profile, liver profile, blood counts. The 10-year coronary heart disease (CHD) was calculated for each patient using the UKPDS risk engine.

Relationship between Fasting Insulin Concentration as a Risk Factor for Cardiovascular Disease and High-Density Lipoprotein Cholesterol Levels in Patients with Chronic Hepatitis C

RAMONA MARIA DRAGUT, EMILIA RUSU, RAMONA CURARU, FLORIN RUSU, ADRIAN CURARU, HORTITU POFESCU, GABRIELA RADULIAN, Pitesti, Romania, Bucharest, Romania.

The objective of this study was to evaluate the association between fasting insulin concentration—as a cardiovascular risk factor—and the high density lipoprotein level (HDL-c) in patients with chronic hepatitis C. Material and Methods: In this cross-sectional study, were included 171 patients from Bucharest, to which were followed anthropometric indexes. Biochemical parameters followed were glucose fasting insulin, glycosylated hemoglobin, lipid profile, liver profile, blood counts. The 10-year coronary heart disease (CHD) was calculated for each patient using the UKPDS risk engine.
Results: The mean age of patients was evaluated 53.14 ± 8.3 years, females representing 53.8% (n=52) of total. Using the UKPDS score 24% (n=44) and 20.5% (n=44) presented moderate and high risk of cardiovascular disease. Levels of fasting insulinemia was significantly high in patients with increase cardiovascular risk (34.41 mg/dl) vs. patients with reduce (43.03 mg/dl) or moderate cardiovascular risk (39.59 mg/dl) (p<0.001). Increased PWV was associated with lower SDNN independent of age, gender, race/ethnicity, BP and BMI (p<0.001). Level of HDL-cholesterol was positively correlated with age (r=0.62, p=0.001), Forns index (r=0.55, p=0.001), BMI-In (r=0.39, p=0.001), smoking status (r=0.52, p=0.001), HbA1c (r=0.41, p=0.001), triglycerides (r=0.43, p=0.001), LDL-c (r=0.43, p=0.001), AST (r=0.33, p=0.001), ALT (r=0.26, p=0.001) and GGT (r=0.31, p=0.001) and negative with LDL (r=0.44, p=0.001) and albumin (r=−0.28, p=0.001).

Conclusions: A higher fasting insulin concentration or hyperinsulinemia was significantly associated with an increased cardiovascular risk. The study suggests that early fasting insulin ascertainment in the patients with HCV may help clinicians identify those who are potentially at high risk of CVD.

### Table
#### Characteristics of the Youth with Type 2 Diabetes Stratified by Their Arterial Stiffness (AS) Status.

<table>
<thead>
<tr>
<th>Variable</th>
<th>AS -</th>
<th>AS +</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>22 ± 4</td>
<td>23 ± 4</td>
<td>0.008</td>
</tr>
<tr>
<td>Systolic Blood Pressure, mm Hg</td>
<td>115 ± 10</td>
<td>121 ± 11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI z-score</td>
<td>1.9 ± 0.4</td>
<td>2.4 ± 0.37</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-cholesterol, mg/dl</td>
<td>43 ± 9</td>
<td>39 ± 9</td>
<td>0.007</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>104 (73, 175)</td>
<td>139 (87, 248)</td>
<td>0.02</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>8.7 ± 4.4</td>
<td>9.5 ± 4.1</td>
<td>0.28</td>
</tr>
<tr>
<td>SDNN, msec</td>
<td>52(38,79)</td>
<td>42(29,62)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

**Supported By:** Centers for Disease Control and Prevention, National Institute of Diabetes and Digestive and Kidney Diseases

---

**441-P**

**Association between Arterial Stiffness and Cardiovascular Autonomic Neuropathy in Youth with Type 2 Diabetes—SEARCH for Diabetes in Youth Study**

MAMTA JAISWAL, JASMIN DIVERS, DANA DABELEA, JEAN M. LAWRENCE, GRACE KIM, ANGELA D. LIESE, ELAINE M. URBINA, Ann Arbor, MI; Winston-Salem, NC; Aurora CO; Pasadena, CA; Seattle, WA; Columbia, SC; Cincinnati, OH.

Accelerated vascular aging in youth with type 2 diabetes (T2D) makes them vulnerable for a cardiovascular event in early adulthood. We explored the relationship between increased arterial stiffness (AS) and reduced heart rate variability (HRV) in youth with T2D.

193 youth with T2D (age 22 ± 4 years, duration 8 ± 2 years, HbA1c 8.9 ± 4.4%, 40% non-Hispanic black) enrolled in the SEARCH study had PWV (pulse wave velocity carotid-femoral segment) and HRV [standard deviation of the natural RR interval (SDNN), root mean square successive difference (RMSSD)] of normal RR rate variability (HRV) in youth with T2D.

**Results:** Youth with increased AS were older, had higher blood pressure (BP), BMI, triglycerides and lower LDL-c (P ≤ 0.05) (Table). In linear regression analyses, increased PWV was associated with lower SDNN independent of age, gender, race/ethnicity, BP and BMI (β = −0.03, SE = 0.02, P = 0.04). However, the association was attenuated and non-significant when controlled for triglyceride suggesting that the relationship between AS and HRV is mediated partly by dyslipidemia.

Early subclinical atherosclerosis was associated with cardiovascular autonomic neuropathy in young people with T2D which could potentially increase the risk of early cardiovascular events. Interventions targeting the risk factors for AS and CAN are needed.

---

**443-P**

**Albuminuria Is More Closely Associated With Vascular Endothelial Function than eGFR in Type 2 Diabetes with Diabetic Kidney Disease**

YOSHINORI KAKUTANI, MASANORI EMOTO, YUKO YAMAZAKI, KOKA MOTOYAMA, TOMOAKI MORIYAMA, KATSUHITO MORI, SHINYA FUKUMOTO, ATSUSHI SHIOI, TETSUO SHOJI, MASAAKI INABA, Osaka, Japan.

**Diabetic kidney disease (DKD), defined by decreased estimated glomerular filtration rate (eGFR) and/or existence of albuminuria, is an important issue for the prevention of cardiovascular disease (CVD) as well as end-stage renal disease. Recently, attention has been focused on the discordance between albuminuria and decreased eGFR in DKD in various clinical situations. However, clinical implication of albuminuria and/or eGFR on subclinical atherosclerosis does not fully remain clear as yet. The present study aims to investigate the association of albuminuria (ACR, mg/gCre) or decreased eGFR (mL/min/1.73m2) with endothelial dysfunction as an early surrogate marker of CVD in type 2 diabetic patients (T2D) with DKD. Six-hundred thirty-three patients (male, 383; median age 64 years, duration 10 years, HbA1c 8.4%) were enrolled. Flow-mediated dilatation (FMD, %) of brachial artery was measured by novel ultrasound equipment (UNEX EP™, Nagoya). All subjects were distributed in each stage of ACR or eGFR as follows: ACR, 425 (67.1%) subjects in A1 stage (<30), 101 (15.9%) in A2 (>30-60), 107 (16.9%) in A3 (>60); eGFR, 392 (61.9%) subjects in G1/G2 stage (<60), 118 (18.6%) in G3a (45-60), 63 (10.0%) in G3b (30-45), 60 (9.5%) in G4/5 (<30). FMD was found to be significantly lower in order of advanced stage of albuminuria or eGFR, respectively: 7.1±4.3 (A1), 6.3±3.5 (A2), 5.4±4.0 (A3), p<0.001; 7.3±4.2 (G1/G2), 5.5±3.0 (G3a), 6.7±4.7 (G3b), 5.0±4.3 (G4/5), p<0.001. In multivariate analyses, only log-transformed ACR (β = 0.13, p = 0.005) contributed to FMD independently even after adjustment for known classical risk factors such as age, BMI, HbA1c, and LDL-c, but eGFR did not.

In conclusion, albuminuria is stronger independent determinant to endothelial function than eGFR in T2D patients with DKD. Our findings suggest that albuminuria may be more important than eGFR as a risk factor and/or potential therapeutic target for CVD in these high risk population.
Roles of Histone Deacetylases in Arteriovenous Fistula Failure Under Disturbed Flow

JENG-JUAN CHIU, TUNG-LIN YANG, Miaoli, Taiwan

Chronic kidney disease, which affects 11.9% of adults and its prevalence of the end-stage renal disease (ESRD) is highest in Asia, is a major health problem in the world. More than 90% of the ESRD patients receive hemodialysis, with the creation of hemodialysis vascular access (HVA), including arteriovenous fistula (AVF). Although AVF is the preferred form of permanent hemodialysis access, it still remains significant problems, such as thrombosis, stenosis and vascular access infections. AVF operation has been shown to change hemodynamic environments. However, the relationship between hemodynamic factors and AVF failure remains unclear. By using Doppler ultrasound to detect the flow patterns in human patients with AVF and rat AVF models, we found that flow disturbance with high and oscillatory shear stress (HSS, ~30±100 dyne/cm²) and laminar shear stress (LSS) at 5 dyne/cm² to mimic flow patterns in the pathophysiological and physiological flow environments of human AVF, respectively. Application of HSS to venous ECs induces the association of HDAC-3 with krüppel-like factor 2 (KLF2) to deacetylate KLF2, resulting in the down-regulation of TM. Intra-peritoneal administration of valproic acid (VPA), which is a specific inhibitor of class I HDACs, into AVF rats inhibits the increased formation of stenosis at anastomotic sites. Our findings demonstrate that flow disturbance with HSS can induce HDAC-3 to deacetylate KLF2 and repress TM, and hence contribute to AVF stenosis and failure. Such information may help to generate new approaches for therapeutic interventions against inflammation and thrombosis in AVF in patients.

Supported By: National Health Research Institutes of Taiwan
Acute and Chronic POSTERS

and newer glucose-lowering agents is warranted in this high-risk population. and had a significant number of individuals with suboptimal glucose and lipid
groups were predominantly treated with older glucose-lowering medications
T2D was insulin (92%), followed by metformin (20%), DPP-4 inhibitors (19%)
and 24 months posttransplant individuals with T2D, compared to NODAT, had
individuals with T2D, compared to NODAT and non-DM, were more frequently
excluded. NODAT was defined by the ADA criteria.

Background: Given the increased incidence of post-transplant diabetes and the high cardiovascular burden in transplant recipients, glycemic control
should be targeted aggressively. We aimed to analyze management of pre-
dominantly Hispanic and non-Hispanic black kidney transplant recipients
with type 2 diabetes (T2D) and new onset diabetes after transplant (NODAT).

Methods: We performed a retrospective chart review of all recipients of
kidney transplant from June 01, 2012 until December 31, 2014 in a large uni-

Results: The study included 304 individuals. Fifty percent had T2D and
another 36% developed NODAT during a follow-up of 37 (22-52) months. Individuals
with T2D, compared to NODAT and non-DM, were more frequently treated with statins (76% vs. 65% vs. 39%, respectively; p<0.0001). At 6, 12,
and 24 months posttransplant individuals with T2D, compared to NODAT, had
higher levels of Alc (7.9 ± 1.8 vs. 8.5 ± 1.2, 8.1 ± 1.8 vs. 6.6 ± 1.3%, 8.6 ± 2.1 vs. 6.6 ± 1.1%, respectively; p<0.0001 for all comparisons) and less fre-
quently reached goal of <7% (33 vs. 80%, 26 vs. 71%, 14 vs. 79%, respectively,
p<0.0001 for all comparisons). Most frequent glucose-lowering treatment in
T2D was insulin (92%), followed by metformin (20%), DPP-4 inhibitors (19%)
and sulfonilurea (11%), while NODAT was treated most frequently with diet
only (43%), followed by metformin (20%) and DPP-4 inhibitors (20%).

Conclusions: While metabolic control was better in NODAT than T2D, both
groups were predominantly treated with older glucose-lowering medications
and had a significant number of individuals with suboptimal glucose and lipid
management. Earlier and more aggressive treatment with cardio-protective
and newer glucose-lowering agents is warranted in this high-risk population.

Skin Autofluorescence Predicts Macrovascular Events in Type 1 Diabetes
CHRISTELLE BLANIC-BISSON, FRITZ-LINE VELAYOUDOM CEPHISE, CATHERINE HELMER, LAURENCE BLANCO, KAMEL MOHAMMEDI, MARIE MONLUN, VIN-
CENT RIGALLEAU, Pessac, France; Abyrnes, Guadeloupe, Bordeaux, France

Advanced Glycation end-products play a role in diabetic vascular compli-
cations. Their optical properties allow to non invasively evaluate their accu-

Table. Progression of CAD from Baseline to 7 Years in the Two Treatment Groups.

<table>
<thead>
<tr>
<th>T2D population</th>
<th>Baseline 7 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>MULTI (n=30)</td>
<td>STAND (n=26)</td>
</tr>
<tr>
<td>MULTI (n=30)</td>
<td>STAND (n=26)</td>
</tr>
</tbody>
</table>

CAD progression: Extent Score 0.08±0.07 0.07±0.12 0.06±0.08 0.10±0.11 0.30*
Severity Score 0.74±0.34 0.83±1.17 0.87±0.98 1.18±1.06 1.02*
*p for between-group difference in change from baseline to 7 years

Supported By: South Eastern Norway Regional Health Authority
The microvascular perfusion is modulated by physiological functions, which have been associated with specific frequency ranges. Although cardio-respiratory interactions have been widely analyzed at a macrocirculation level, only few studies have been conducted with the aim to understand the effect of breathing on the peripheral circulation. Diabetic microangiopathy is characterized by structural and functional alterations of the blood microvessels, which reflect in a modification of the physical properties of peripheral microvascular beds, such as vascular stiffness. A wavelet phase coherence (WPC) analysis was performed to elucidate the time-phase relationship between the respiratory activity and vascular-dependent features of the peripheral pulse, reconstructed by means of a novel multi-Gaussian modeling algorithm. The present WPC analysis was conducted on a group of 24 healthy volunteers, mean age 30±15 years, in comparison with 21 type 1 diabetic (T1D) subjects, mean age 26±3 years, in order to detect the effects of T1D on the physiological coupling between breathing and microcirculation. The peripheral cutaneous perfusion was assessed on the pulp of the index finger with the laser Doppler flowmetry (LDF) technique, while the respiratory signal was simultaneously recorded with a wearable chest band. In 17 out of the 24 control subjects involved (i.e., 71%), significant WPC values were identified in the respiratory frequency range (0.145-0.6 Hz), with respect to the area beneath the diastolic portion of the peripheral pulse (median WPC: 77.9%). This outcome indicates that the diastolic phase of the pulse exhibits a marked periodicity linked to the breathing activity. The analysis conducted on the T1D group highlighted a loss of synchronization, with significant WPC levels found in only 33% of the investigated subjects. These results suggest that the proposed method is able to detect the detrimental effects of T1D on the blood microcirculation.

Cardiovascular Event Hazards over Time in TECOS

M. ANGELINI BETHEL, HARALD SOURA, SUSANNA R. STEVENS, YULIYA LDKH-NYGINA, RENATO D. LOPES, AMANDA ADLER, DARREN K. MCGUIRE, ERIC PETERSON, RURY R. HOLMAN, Oxford United Kingdom, Graz, Austria, Durham, NC, Cambridge, United Kingdom, Dallas, TX

Background: Event accumulation patterns in event-driven trials inform forecasting of trial size and duration. It is hypothesized that trials enroll a healthier cohort who have lower early cardiovascular (CV) event rates that forecast the trial size and duration. Weibull models show whether hazards for these CV events were increasing (shape parameter>1), decreasing (<1), or constant (=1) over time: Hazard rate over time. Weibull shape parameter estimation was conducted on the intention-to-treat population. Results: The Figure shows hazard rate over time. Weibull shape point estimates [95% CI] were MACE-4 0.96 (0.92, 1.01), CV death 1.08 (1.01, 1.16), F/NMFI 0.96 (0.89, 1.03), F/NFSt 0.93 (0.85, 1.03), UA 0.90 (0.79, 1.01), HF 0.98 (0.90, 1.08). Annual event rates (per 100 pt-years) were CV death: 1.5, 1.6, 2.0, 1.9, 2.7; F/NMFI: 2.1, 2.3, 2.8, 3.0, 3.8. Conclusions: Hazard rates were constant for all events except CV death and ACM, which had small significant increased risk over time. Our findings may inform the planning and conduct of future trials in diabetes.

Hyperglycemia is an independent risk factor for the development of respiratory diseases, including influenza infections. Although the lung is a major organ to utilize glucose, the regulation of glucose transport in the healthy and diabetic lung has received little attention. We hypothesized that hyperglycemia would predispose diabetic mice to alterations in pulmonary glucose transport and pulmonary complications during influenza A infection. To test this hypothesis, we used a streptozotocin-induced type 1 diabetic mouse model (n=8-12/group). A subset of diabetic mice was treated with insulin via a subcutaneous insulin pump to restore euglycemia. After 8 weeks, an additional subset of mice was intranasally infected with influenza A H1N1 (A/PR/8/34; 250 PFU). Viral titer was determined from bronchoalveolar lavage (BAL) fluid by plaque assay. Glucose concentration in BAL fluid was measured spectrophotometrically. Glucose transporter (GLUT) protein content was quantified in whole lung homogenates by Western blotting. Both infected and uninfected diabetic mice had higher glucose concentrations in BAL fluid than their control or insulin-treated counterparts (p<0.05). There was a trend towards a decrease in protein content of GLUT4 (the major insulin-sensitive isoform) and GLUT1 (a basal isoform) in the diabetic lung (p=0.1). Total protein content of GLUT12 (a novel isoform) was increased in the diabetic lung (p<0.05). Diabetic mice possessed a significantly higher percentage of lymphocytes in their BAL fluid (p<0.05). Glut protein content and lymphocyte alterations were rescued when mice were treated with insulin. Influenza-infected diabetic mice also had a higher percentage of lym-
High Serum Branched-Chain Amino Acids Level Independently Predicts Incident Heart Failure—The Hong Kong Diabetes Register

LEI-LING LIU, ERIC S.H. LAU, ANDREA LUK, ELAINE CHOW, HEUNG MAN LEE, RONALD C. MA, JULIANA C. CHAN, ALICE P. KONG, Hong Kong, China

Background: Obesity predicts cardiovascular (CV)-renal disease. Contrary to claims that branched-chain amino acids (BCAA)-rich diet/supplements may improve weight and insulin resistance, recent data suggest impaired oxidation of BCAA (leucine, isoleucine and valine) may contribute to CV-renal disease. We examined the associations of serum BCAA, obesity and CV-renal events in a prospective Chinese T2D cohort (1994-2007).

Method: We measured serum total BCAA in 579 and 566 patients (top and bottom BMI quintiles respectively) using the colorimetric ELISA kit. Patients were monitored for clinical outcomes with data censored on May 2015. We analysed the effect of serum BCAA on incident CV-renal events using multivariate Cox regression.

Results: At baseline, obese group had shorter T2D duration, worse clinical profile and higher serum BCAA than lean group. After 11 years of follow-up, obese group had higher incidence of heart failure (HF), chronic kidney disease and any CV disease than the lean group. In all patients, every unit increase in ln (BCAA) elevated the risk of incident HF by 64% (hazard ratio [HR] 1.64, 95% CI 1.01-2.66).

Conclusions: Serum BCAA independently predicted incident HF in T2D population even after adjustment for obesity. The associations of this biomarker with dietary patterns and clinical outcomes will provide new insights regarding the health impacts of nutrition.

Table.

<table>
<thead>
<tr>
<th>Model</th>
<th>Event</th>
<th>HR (95% CI)</th>
<th>P-value</th>
<th>Event</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>Adjusted for age, sex, T2D duration.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>Model 1 + A1c, systolic BP, LDL-cholesterol, log (triglyceride), BMI top and lowest quintiles (0.1), log (ACR), baseline eGFR, use of insulin, RAS inhibitors, oral blood glucose/lipid lowering agents, smoking status.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Support: By: Hong Kong Association for the Study of Obesity; Hong Kong Society of Endocrinology, Metabolism and Reproduction

Impact of Type 2 Diabetes Mellitus and Myocardial Perfusion on Long-term Risk of Type 2 Diabetes Mellitus and All-cause Mortality Following Interventional Treatment of ST-elevation Myocardial Infarction

ANDEZ TOMASIK, KATARZYNA NABDASIK, HANNA KWIENDACZ, TOMASZ SAWCZYN, MICHAL KUKLA, EDYTA RADZIK, KATARZYNA PISIO, TOMASZ MIYCHRAK, JANUSZ GUMPRECHT, WŁADYSŁAW GRZESZCZAK, EWA NOW-ALANY-KOZIELSKA, ZABROF, Poland, Katwice, Poland

Patients with type 2 diabetes mellitus (T2DM) who undergo primary percutaneous coronary intervention (pPCI) for ST-elevation myocardial infarction (STEMI) have worse myocardial perfusion than normoglycemic patients. It is not known whether these factors combined influence prognosis in term of heart failure (HF) and/or all-cause mortality. We aimed to evaluate the impact of T2DM and myocardial perfusion on long-term risk of HF and/or all-cause mortality following interventional treatment of STEMI. 406 STEMI patients (104 with T2DM) treated with pPCI were enrolled into the study. Myocardial perfusion was reassessed with myocardial blush grade (MBG), Quantitative myocardial Blush Evaluation (QuBe), resolution of ST-segment elevation (STI). Follow-up data was collected during 6 years. 23.1% patients with T2DM developed HF vs. 16.9% without T2DM (P=NS). 34.6% of patients with T2DM have died vs. 14.9% patients without T2DM (P=0.000). Patients with T2DM and HF have had the highest mortality rate of 75%. Survival of patients with T2DM in relation to QuBe score is presented in the Figure. There was no difference in myocardial perfusion assessed by STI. T2DM and diminished myocardial perfusion increase the risk of HF and/or all cause death in 6 years follow-up.

Figure.

Effects of Early Intensive Insulin Therapy on Endothelial Progenitor Cells in Patients with Newly Diagnosed Type 2 Diabetes

HONGDONG WANG, YAN BI, FANGGEN LIU, Nanjing, China

Objective: Reduced level of endothelial progenitor cells (EPCs) is a critical event in the pathogenesis of vasculopathy in type 2 diabetes. This study aimed to investigate circulating EPCs alteration in newly diagnosed type 2 diabetic patients and how they are affected by early intensive insulin therapy.

Methods: Twenty-one newly diagnosed type 2 diabetic patients and 22 control subjects matched by age, gender, and BMI were enrolled. All of the diabetic patients received intensive insulin therapy. EPC numbers were assessed by flow cytometry based on the expression of CD34, CD133, and kinase insert domain-containing receptor.

Results: Level of EPC was higher in diabetic patients compared to control subjects (0.07±0.08% vs. 0.16±0.17%, P=0.01). Notably, EPC number was significantly decreased after therapy (0.00±0.06%, P=0.01 vs. pre-treatment). Level of vascular endothelial growth factor (VEGF), a major contributor of EPC mobilization, was significantly higher in diabetic patients compared to control subjects (28.34±9.15 vs. 17.9±1.76, P=0.002) and decreased dramatically after insulin therapy (21.0±4.64, P=0.003). Moreover, compared with control subjects, pro-inflammatory cytokines were significantly higher in diabetic patients (TNF-α 19.74±1.65 vs. 15.7±2.16, P=0.01; IL-1β 14.04±5.6 vs. 9.41±1.94, P=0.017; IFN-γ 16.47±3.37 vs. 11.7±1.39, P=0.013) and decreased markedly after insulin therapy (17.2±1.78, P=0.009; 10.8±1.35, P=0.001; 13.7±2.21, P=0.001).

Conclusions: These results showed that type 2 diabetes is associated with increased circulating EPC level at the onset of diabetes, indicating increased compensatory mobilization. Additionally, early intensive insulin therapy exerts a preserved effect on EPC level partly through improving inflammation status, thereby implying a putative long term beneficial effect on vascular integrity via suppressing excessive EPC exhaustion.

Impact of Type 2 Diabetes Mellitus and Myocardial Perfusion on Long-term Risk of Type 2 Diabetes Mellitus and All-cause Mortality Following Interventional Treatment of ST-Elevation Myocardial Infarction

ANDEZ TOMASIK, KATARZYNA NABDASIK, HANNA KWIENDACZ, TOMASZ SAWCZYN, MICHAL KUKLA, EDYTA RADZIK, KATARZYNA PISIO, TOMASZ MIYCHRAK, JANUSZ GUMPRECHT, WŁADYSŁAW GRZESZCZAK, EWA NOW-ALANY-KOZIELSKA, ZABROF, Poland, Katwice, Poland

Patients with type 2 diabetes mellitus (T2DM) who undergo primary percutaneous coronary intervention (pPCI) for ST-elevation myocardial infarction (STEMI) have worse myocardial perfusion than normoglycemic patients. It is not known whether these factors combined influence prognosis in term of heart failure (HF) and/or all-cause mortality. We aimed to evaluate the impact of T2DM and myocardial perfusion on long-term risk of HF and/or all-cause mortality following interventional treatment of STEMI. 406 STEMI patients (104 with T2DM) treated with pPCI were enrolled into the study. Myocardial perfusion was reassessed with myocardial blush grade (MBG), Quantitative myocardial Blush Evaluation (QuBe), resolution of ST-segment elevation (STI). Follow-up data was collected during 6 years. 23.1% patients with T2DM developed HF vs. 16.9% without T2DM (P=NS). 34.6% of patients with T2DM have died vs. 14.9% patients without T2DM (P=0.000). Patients with T2DM and HF have had the highest mortality rate of 75%. Survival of patients with T2DM in relation to QuBe score is presented in the Figure. There was no difference in myocardial perfusion assessed by STI. T2DM and diminished myocardial perfusion increase the risk of HF and/or all cause death in 6 years follow-up.

Figure.
Patients who were dependent at discharge had similar prevalence of T2DM (50.4% were dependent at discharge and 43.4% died during hospitalization. 95% confidence interval (CI) 1.10-3.79, p<0.05) and NIHSS at admission (RR 1.16, 95% CI 1.09-1.23, p<0.001).

Independent risk factors for pneumonia were obesity (relative risk (RR) 2.05, p<0.05) and NIHSS at admission (RR 1.16, 95% CI 1.09-1.23, p<0.001).

The outcome of pneumonia in patients admitted with acute ischemic stroke is unclear. The aim of the present study was to evaluate this association.

Patients and Methods: We prospectively studied 922 consecutive patients admitted with acute ischemic stroke (42.2% males, age 79.6±6.9 years). The severity of stroke was assessed at admission with the National Institutes of Health Stroke Scale (NIHSS). The outcome was assessed with dependency rates at discharge (modified Rankin scale 2-5) and in-hospital mortality.

Results: During hospitalization, 113 patients developed pneumonia. Patients who developed pneumonia had higher fasting plasma glucose (FPG) levels at the second day of hospitalization than patients who did not develop pneumonia (7.4±3.4 and 6.3±2.6 mmol/L, respectively; p<0.005) whereas the prevalence of T2DM and HbA1c levels did not differ between the two groups. Independent risk factors for pneumonia were obesity (relative risk (RR) 2.05, 95% confidence interval (CI) 1.10-3.79, p<0.05) and NIHSS at admission (RR 1.16, 95% CI 1.09-1.23, p<0.001). Among patients who developed pneumonia, 50.4% were dependent at discharge and 43.4% died during hospitalization. Patients who were dependent at discharge had similar prevalence of T2DM and similar FPG and HbA1c levels with patients who were independent at discharge. Patients who died during hospitalization had higher FPG levels than patients who were discharged (8.3±4.4 and 6.7±2.3 mmol/L, respectively; p<0.05) whereas the prevalence of T2DM and HbA1c levels did not differ between the two groups. Independent risk factors for in-hospital mortality were diastolic blood pressure at admission (RR 1.05, 95% CI 1.01-1.09, p<0.005) and NIHSS at admission (RR 1.16, 95% CI 1.09-1.23, p<0.001).

Conclusions: T2DM does not appear to be associated with the incidence or the outcome of pneumonia in patients admitted with acute ischemic stroke.

Bone and Vascular Health in Postmenopausal Women with Type 1 Diabetes

VIRAL N. SHAH, PRAKRITI JOSHEE, RACHEL M. SIPPY, JANET K. SNELL-BERGEON, Aurora, CO

The risk for cardiovascular (CV) disease and osteoporotic fractures is higher in postmenopausal women with type 1 diabetes (T1D). However, it is unclear whether these processes have common risk factors. We examined the associations between bone mineral density (BMD), trabecular bone score (TBS), and CV risk measures in 47 postmenopausal women with T1D (62 years, diabetes duration; 41 years and A1c 7.8%) and 51 postmenopausal women without diabetes (64 years and A1c 5.5%).

Bone mineral density, serum creatinine, calcium, 25-DH-D, parathyroid hormone (PTH) and bone turnover markers (BTMs) were similar between two groups. T1D postmenopausal women had lower left femoral neck and distal forearm BMD, and subcortical viability index (SVI) and higher augmented pressure (AP) and carotid intima media thickness (cIMT) compared to controls (Table). HbA1c was negatively correlated with distal forearm BMD, TBS and SVI and positively correlated with AP. Total cholesterol and LDL-C were associated with arterial stiffness but not with BMD. PTH and BTMs were associated with lower BMD but not with CV risk measures. Urinary microalbumin was inversely correlated with distal forearm BMD and TBS, and positively correlated with AP and cIMT.

T1D is associated with lower femoral neck and distal forearm BMD and higher arterial stiffness and cIMT. Urine microalbumin was the only factor linked to both low BMD and high CV risk.

Compliation—Macrovascular—Atherosclerotic Cardiovascular Disease and Human Diabetes

Type 2 Diabetes Mellitus Is Not Associated with the Incidence or the Outcome of Pneumonia in Patients with Acute Ischemic Stroke

MARIANTHI PAPAGIANNI, KONSTANTINOS TZIGMALOS, STELLA MARIA ANGELOPOULOU, STELLINA ALKAGIET, TRIANTAFYLLOS DIDANGELOS, CHRISTOS SAVOPOULOS, APULISTOS I. HATZITOLIOS, Thessaloniki, Greece

Background/Methods: The association between T2DM and the incidence and outcome of pneumonia in patients with acute ischemic stroke is unclear. The aim of the present study was to evaluate this association.

Patients and Methods: We prospectively studied 922 consecutive patients admitted with acute ischemic stroke (42.2% males, age 79.6±6.9 years). The severity of stroke was assessed at admission with the National Institutes of Health Stroke Scale (NIHSS). The outcome was assessed with dependency rates at discharge (modified Rankin scale 2-5) and in-hospital mortality.

Results: During hospitalization, 113 patients developed pneumonia. Patients who developed pneumonia had higher fasting plasma glucose (FPG) levels at the second day of hospitalization than patients who did not develop pneumonia (7.4±3.4 and 6.3±2.6 mmol/L, respectively; p<0.005) whereas the prevalence of T2DM and HbA1c levels did not differ between the two groups. Independent risk factors for pneumonia were obesity (relative risk (RR) 2.05, 95% confidence interval (CI) 1.10-3.79, p<0.05) and NIHSS at admission (RR 1.16, 95% CI 1.09-1.23, p<0.001). Among patients who developed pneumonia, 50.4% were dependent at discharge and 43.4% died during hospitalization. Patients who were dependent at discharge had similar prevalence of T2DM and similar FPG and HbA1c levels with patients who were independent at discharge. Patients who died during hospitalization had higher FPG levels than patients who were discharged (8.3±4.4 and 6.7±2.3 mmol/L, respectively; p<0.05) whereas the prevalence of T2DM and HbA1c levels did not differ between the two groups. Independent risk factors for in-hospital mortality were diastolic blood pressure at admission (RR 1.05, 95% CI 1.01-1.09, p<0.005) and NIHSS at admission (RR 1.16, 95% CI 1.09-1.23, p<0.001).

Conclusions: T2DM does not appear to be associated with the incidence or the outcome of pneumonia in patients admitted with acute ischemic stroke.

Low Prevalence of Peripheral Arterial Disease in Type 2 Diabetes Patients in North India

BRUJ M. MAKKAR, JUGAL K. SHARMA, SHALINI JAGGI, KIRTI SOOTA, JR., VIPUL GUPTA, GIRISH KHURANA, SR., Delhi, India, New Delhi, India, Bahadurgarh, India

Introduction: Peripheral Arterial Disease (PAD) is a major macrovascular complication of type 2 diabetes (T2D). Though data is limited, studies have indicated a lower prevalence of PAD in Indian diabetes patients as compared to western population. Present study assessed prevalence of PAD in T2D patients in Delhi, North India. Methodology: This study is a retrospective analysis of patient records of T2D patients. A total of 1000 patient were screened, 195 patients were excluded due to incomplete data and 805 patients were included in the study. Diagnosis of PAD was based on ankle brachial index (ABI) measurement. An ABI value of <0.9 indicated as PAD.

Results: Study population consisted of 470 male and 335 female T2D patients (n=805), group 22 to 83 years. PAD (ABI <0.9) was present in 12 patients (1.49%), 9 males (75% of PAD) and 3 females (25% of PAD). Diabetes patients with PAD had a higher mean age (57.68 ±10.96 vs. 50.97 ±10.03 years) a longer duration of diabetes (12.67 ±7.9 vs. 8.06 ±8.06 years,
Acute and Chronic Complications—Macrovascular—Atherosclerotic Cardiovascular Disease and Human Diabetes

**463-P**

Effect of Hypercholesterolemia on the Characteristics of Cerebral Microvasculature

Yusuke Toda, Yasushi Ishigaki, Monika, Japan

Aim: It remains unclear whether the increase of LDL cholesterol (LDL-C) is a risk factor for cerebral vascular disease (CVD). To clarify the effects of hypercholesterolemia on cerebral small vessel disease (SVD), we investigate the characteristics of microvasculature including lenticulostrate arteries (LSA) using high resolution brain magnetic resonance imaging (MRI) in subjects with familial hypercholesterolemia (FH).

Methods: Twenty-seven patients with FH and 25 patients with type 2 diabetes (DM), 25 healthy controls underwent 7Tesla (7T) brain MRI. The prevalence of SVD and LSA structural changes, vessel wall plaque images were determined in each group.

Results: The prevalence of SVD, including white matter hyperintensities and lacunar infarctions, significantly increased in DM compared with both FH and controls. In addition, the average numbers of stems of LSA were significantly smaller in DM than FH as well as controls. Interestingly, both SVD prevalence and LSA structural changes showed no difference between FH and controls. Next, we examined the vessel wall imaging analyses of middle cerebral arteries (MCA) and vertebral-basilar arteries (VA-BA). The prevalence of vessel wall plaque on both horizontal segment of MCA (FH vs. controls; 51.8% vs. 20.0%, p<0.05) and VA-BA (37.0% vs. 12.0%, p<0.05) were significantly higher in FH than controls.

Conclusion: The prevalence of SVD and LSA structural impairment definitely increased in DM, suggesting that DM was strong risk for CVD compared to hypercholesterolemia. On the other hand, the prevalence of vessel wall plaque on MCA and VA-BA were significantly high in FH compared to controls. These results suggested long-term increase of LDL-C induced the plaque formation in cerebral microvasculature. The study enables us to investigate the characteristics of cerebral microvasculature prior to the development of SVD, leading to earlier interventions aimed at the prevention of atherosclerotic events.

**464-P**

Association of Serum Sestrin2 Level with Metabolic Risk Factors in Newly Diagnosed Drug-Naive Type 2 Diabetes


Objective: Previous in vitro and in vivo experimental studies have shown that Sestrin2 attenuates oxidative stress and the pro-inflammatory pathway, resulting in improving metabolic homeostasis. However, the relationship between circulating Sestrin2 concentration and cardiometabolic risks in humans has not been explored.

Methods: Sestrin2 concentration was measured in 240 subjects (46 non-diabetic and 194 diabetic) using an enzyme-linked immunosorbent assay, and the associations between Sestrin2 level and various cardiometabolic risk factors including body composition, insulin resistance, and atherosclerosis was assessed.

Results: Sestrin2 concentration showed a trend of increasing in subjects over 50 years and lower BMI (24.82kg/m2 vs. 24.55±5.87 kg/m2, p=0.0066) as compared to non-diabetic patients. More patients with PAD had hypertension (58.33% vs. 47.79%, p=0.06) and coronary artery disease (16.67% vs. 7.44%, p=0.008) which, however, were not statistically significant. PAD patients had significantly higher levels of total cholesterol (198.75±59.39 vs. 192.33±44.71mg/dl, p=0.0055) and LDL cholesterol (126.66±40.48mg/dl, p=0.039). No difference was seen in triglyceride levels (165.67±70.92mg/dl vs. 165.4±101.14, p=0.90) and ALT and A1c levels (8.97±3.08 vs. 9.08±2.54, p=0.87) in two groups.

Conclusion: Our study shows that prevalence of PAD in T2D patients in Delhi, North India, is much lower than that reported in stem populations (~20%) and from south India (6.3%). Prevalence of PAD was higher in patients with higher age, longer duration of diabetes, lower BMI, higher total and LDL cholesterol.

**465-P**

Gut Incretin Release as a Mediator of Metabolic Effects of Metformin in Type 2 Diabetic Patients with Chronic Heart Failure

Eva Stolarikova, Jan Kopecky, Jr., Jiri Veleba, Katerina Velebova, Lenka Belinova, Vojtech Melehnovsky, Jan Kopecky, Sr., Terezie Pelikanova, Prague, Czech Republic

Introduction: Metformin (MET) is a first choice drug used in patients with type 2 diabetes (DM). Treatment with MET in patient with DM and heart failure (HF) is associated with better cardiovascular outcomes, but mechanisms of MET-mediated effects are unexplained. Our aim was to evaluate the effects of MET on substrate metabolism, cardiac function and structure in patient with DM and HF.

Methods: 40 patients with DM and stable chronic HF (age: 59 ± 9 years) were studied in a random sequence cross-over clinical study testing the effect of 3-month usage of MET vs. placebo. The subjects were randomized to MET (2 g/day) or to placebo group. After the three months of treatment the medication was changed and the treatment continued for next 3 months. At the beginning and the end of each intervention period (3 times in total) the panel of various metabolic and cardiovascular tests was done: echocardiography, sputrometry and meal test with evaluation of several variables like insulin level (~GLP-1 and peptide YY) and parameters of oxidative stress (MCP-1, TNFα).

Results: Compared to placebo, MET was accompanied with significantly higher increase of selected gut-related hormones. GLP-1 area-under-curve increased during the meal test (MET vs. PL: 857.39±869.57 vs. 568.92±4580.79pmol.hour11; p<0.01). Also the peptide YY area-under-curve increased during the meal test (MET vs. PL: 29809.67±13442.42 vs. 23636.21±8183.08pmol.hour11; p<0.05). MCP-1 showed inconsistent trend to increase during meal test. Fasted levels of TNFα were higher after MET, but there was no change during the meal test compared to placebo. MET therapy led to reduction of HbA1c (~p<0.001) and reduced glucose area-under-curve (~p<0.01) during glucose tolerance test. MET had neutral effect on cardiac structure and function.

Conclusions: Our results suggest that metabolic effects of MET might be mediated by improvement of gut endocrine function. MET had neutral effect on cardiac function or structure.

Supported By: ADA-Supported Research

**466-P**

Novel “Dual Hit” Rat Model of Diabetic Cardiomyopathy

Louise Thisted, Ross T. Lindsay, Keld Fosgerau, Thomas Secher, Morten B. Thomsen, Thomas Jepsersen, Andrew J. Murray, Philip J. Pedersen, Niels Vrang, Lisbeth N. Fank, Tanja X. Pedersen, Nora E. Zois, Copenhagen, Denmark

The pathogenesis of diabetic cardiomyopathy (DC) is poorly understood and new drugs targeting the myocardium are absent. This may be ascribed to the failure of available pre-clinical models to recapitulate essential clinical features of DC and heart failure. We hypothesized that the combination of experimental diabetes and pharmacologically induced cardiac stress might provide a novel rat model displaying a distinct profile of DC. Noninsulin dependent type 1 like diabetes was induced by partial pan-creatokymy (Pxn). Pronounced hyperglycemia was established within two weeks (blood glucose levels of 23.3 ± 3.7 mM). Five weeks post Px or sham surgery, vehicle or the sympathomimetic agent, isoproterenol (Iso, 1 mg/kg, 2 g/day) or to placebo group. After the three months of treatment the mediation was changed and the treatment continued for next 3 months. At the beginning and the end of each intervention period (3 times in total) the panel of various metabolic and cardiovascular tests was done: echocardiography, sputrometry and meal test with evaluation of several variables like insulin level (~GLP-1 and peptide YY) and parameters of oxidative stress (MCP-1, TNFα).

Results: Compared to placebo, MET was accompanied with significantly higher increase of selected gut-related hormones. GLP-1 area-under-curve increased during the meal test (MET vs. PL: 857.39±869.57 vs. 568.92±4580.79pmol.hour11; p<0.01). Also the peptide YY area-under-curve increased during the meal test (MET vs. PL: 29809.67±13442.42 vs. 23636.21±8183.08pmol.hour11; p<0.05). MCP-1 showed inconsistent trend to increase during meal test. Fasted levels of TNFα were higher after MET, but there was no change during the meal test compared to placebo. MET therapy led to reduction of HbA1c (~p<0.001) and reduced glucose area-under-curve (~p<0.01) during glucose tolerance test. MET had neutral effect on cardiac structure and function.

Conclusions: Our results suggest that metabolic effects of MET might be mediated by improvement of gut endocrine function. MET had neutral effect on cardiac function or structure.

Supported By: ADA-Supported Research

Moderated Poster Discussion

ADA-Supported Research
**467-P**

Impaired Gastric Emptying Is Associated with a Higher Incidence of Coronary Heart Disease in Subjects with Diabetes

SEON-YOUNG PARK, JIN OOK CHUNG, DONG HYEOG CHO, DONG JIN CHUNG, MIN YOUNG CHUNG, Gwangju, Republic of Korea

Results: Impaired gastric emptying is observed in long-standing diabetic patients. To date, there is limited information on cardiovascular events in diabetic subjects with upper gastrointestinal (UGI) symptoms according to the presence of impaired gastric emptying. The aim of this study was to identify cardiovascular events after gastric emptying study in diabetic subjects with UGI symptoms. This study collected data from 160 diabetic subjects (23 with type 1 diabetes and 137 with type 2 diabetes) with UGI symptoms who had undergone gastric emptying scintigraphy from 2001 to 2016. We gathered data on the incidence of cardiovascular events (coronary heart disease and ischemic stroke) after gastric emptying study. There were 56 diabetic subjects with normal gastric emptying and 94 diabetic subjects with impaired gastric emptying (58 with delayed gastric emptying and 36 with rapid gastric emptying). During 7.5 years of follow-up, 22.5% of subjects (36/160) developed the cardiovascular events (19 with coronary heart disease, 12 with ischemic stroke and 5 with both). The incidence of coronary heart disease was higher in the subjects with impaired gastric emptying (4.2% at 1 year, 10.6% at 3 years, and 12.7% at 5 years) than those with normal gastric emptying (2.4% at 1 year, 3.6% at 3 years and 4.8% at 5 years p=0.039). Our results showed that diabetic subjects with impaired gastric emptying had higher incidence of coronary heart disease than those with normal gastric emptying. This study may warrant a more careful cardiovascular assessment with a high index of suspicion for possible events in management of diabetic subjects with impaired gastric emptying.

**A Comparative Study of the Associations between Modified Low-Density Lipoproteins and Vascular Function in African-American Diabetic Patients**

AJIBOLA M. ADEDAYO, AYOBAMI ELUVOLE, FASIK A. TEDA, ARYE KREMER, NICOLE MASTROIANNI, CARL ROSENBERG, PAUL DREZEN, JOHN LAROSA, LOUIS SALZCIGLIO, MOHAMED BOUTJIDI, MARY ANN BANKRU, CLINTON BROWN, MORO SAJFU, JASON LAZAR, AHMED BAKILLAH, Brooklyn, NY

**Background:** LDL plays a key role in development and progression of atherosclerosis. Elevated LDL amplifies the atherosclerotic process but the significance of modified LDL in pathogenesis of vascular complications is unclear. We aimed to assess plasma modified LDL levels and their relationship with vascular function in African-American diabetic patients.

**Methods:** 125 patients with type 2 diabetes were enrolled. Levels of glycated LDL (g-LDL), carbamylated LDL (c-LDL), nitrated LDL (n-LDL) and oxidized LDL (o-LDL) were quantified by ELISA. Microvascular function was assessed by vascular reactivity index (VRI), which assesses changes in digital temperature before and after release of arterial cuff occlusion. Carotid-femoral pulse wave velocity (PWV) assessed arterial stiffness using applanation tonometry. B-mode ultrasound image analysis assessed Carotid intima-media thickness (CIMT). Patient population was divided into well-controlled: HbA1c ≤7.0%, N=54; poorly-controlled: HbA1c >7.0%, N=71.

**Results:** Age 66±9 years; 84% Female, 80% Hypertension, 90% Dyslipidemia and 15% CKD. HbA1c level 8±2.2%, diabetes duration 10.2±9.7 years. Mean plasma g-LDL, c-LDL, n-LDL and o-LDL were 15.5±5.4 mg/dL, 15.6±5.1 mg/dL, 23.3±3.3 mg/dL, and 16.7±3.3 mg/dL. Ox-LDL was positively correlated with CIMT in well-controlled patients (r=0.45, p<0.001), but not in poorly-controlled (r=0.12, p=0.30). Multi-regression analysis revealed ox-LDL was independently associated with CIMT, but neither with PWV nor VRI after adjustment for variables such as age, gender, weight, smoking, total cholesterol, HDLc, triglycerides, and LDLc (p=0.033, p=0.012, r=0.38).

**Conclusion:** Ox-LDL offered better predictive value for CIMT in well-controlled patients than other forms of modified LDL. These data favor ox-LDL as potential marker to identify diabetic patients at risk of developing atherosclerotic vascular complications.

**Supported By:** New York State Department of Health

**ADA-Supported Research**

**Moderated Poster Discussion**

**WITHDRAWN**

---

**468-P**

The Role of Epicardial Adipose Tissue Lymphocytes in Low-Grade Inflammation and Coronary Artery Disease

MILOS MRAZ, ANNA CINKA-JZLOVA, ZDENA LACIWOVA, JANA KLOUKOVA, HELENA KRATOCHVLOVA, MICHAL LIPS, PETR KOPECKY, MICHAL FURIZKA, JAN ORLOVSKY, MARTIN HAVLICK, Prague, Czech Republic

Lymphocytes play a role in the development of adipose tissue inflammation. Epicardial adipose tissue was shown to be a potential source of inflammatory mediators contributing to coronary atherosclerosis. The aim of the study was to assess lymphocyte content in peripheral blood, subcutaneous (SAT) and epicardial adipose tissue (EAT) in subjects with coronary artery disease (CAD) along with the effects of elective cardiac surgery. Twelve subjects without CAD (non-CAD group) and 24 age-, BMI- and HbA1c-matched subjects with CAD were included into the study. Blood, SAT and EAT samples were obtained before and at the end of elective cardiac surgery. Lymphocyte populations were quantified as percent of CD45+ cells using flow cytometry. Subjects with CAD had higher total lymphocyte (CD45+) amount in EAT compared to SAT (32.2±7.45 vs. 11.2±1.34%, p=0.025) with a similar trend observed in non-CAD subjects (29.6±7.61 vs. 10.1±2.01%, p=0.067). CD3+ cells were increased and CD3- cells decreased in EAT of CAD relative to non-CAD group with no difference between EAT and SAT. In both groups EAT showed reduced percentage of NK cells (CD155/CD56+) and elevated B cells (CD19+) relative to SAT (NK cells: 5.96±3.2 vs. 13.2±2.1, p=0.012 for CAD and 5.3±1.97 vs. 13.8±1.2, p=0.022 for non-CAD; B cells: 5.2±2.43 vs. 0.96±0.21%, p=0.039 for CAD and 12.49±5.83 vs. 1.16±0.19%, p=0.016 for non-CAD). CD8+ and NKT (CD16/56+CD3+) cells in EAT correlated positively with fasting glucose and HbA1c, while showing no association in SAT. Cardiac surgery decreased total lymphocytes in peripheral blood, SAT and EAT of both groups, while having only minor effects on lymphocyte subpopulations. To conclude, epicardial adipose tissue in subjects with CAD shows increased amount of total and CD3+ lymphocytes as compared with SAT or non-CAD subjects. These changes could contribute to the development of local inflammation and coronary atherosclerosis.

**Supported By:** Ministry of Health of the Czech Republic (VFN64165, AZV75-28694A)

**WITHDRAWN**

---

**469-P**

**470-P**

**471-P**

**WITHDRAWN**

---

**472-P**

**473-P**

**WITHDRAWN**

---

**474-P**

**475-P**

**WITHDRAWN**

---

**Moderated Poster Discussion: Modulators of Endothelial and Myocardial Dysfunction (Posters: 470-P to 475-P), see page 18.**

**WITHDRAWN**

---

**476-P**

**WITHDRAWN**

---
Intermittent Hypoxia Induces Expression of Epiregulin mRNA via Upregulation of Interleukin-6 in Human Coronary Artery Smooth Muscle Cells

YOJI KOTANI, JING ZHAO, ASAKO ITAYA-HIRONAKA, AKIYU YAMAUCHI, SUMIY AOKAMURATO-TSUCHIDA, MAI MAKINO, SHIN TAKASAWA, MASANORI YOSHIZUMI, Kashiwa, Japan

Sleep apnea syndrome (SAS) is characterized by repetitive episodes of oxygen desaturation and re-saturation, such as intermittent hypoxia (IH), and well known as an independent risk factor for diabetes and atherosclerosis. We previously showed that IH directly induced the proliferation of cultured rat aorta smooth muscle cells through upregulations of epithelial growth factor receptor, especially epiregulin (EREG), and its erbB2 receptor. However, its underlying mechanism remains unclear. On the other hand, we also reported that IH increased interleukin (IL)-6 mRNA in pancreatic beta cells. In this study, we investigated the influence of IH on IL-6 production, and the impact of IL-6 on the expression of EREG, using human coronary artery smooth muscle cells (hCASMC) and in vitro IH system. Quantitative RT-PCR revealed that EREG mRNA was significantly increased by IH, but not by sustained hypoxia. IH also increased expression of IL-6 mRNA in IH cycle dependent manner (3–22 cycles in 1–24 hours). Mature IL-6 increased in IH-exposed cell conditioned medium as similar time-dependent manner as seen in mRNA. We next investigated whether IL-6 increases the expression of EREG mRNA in hCASMCs. The addition of IL-6 (100 ng/mL) induced a significant upregulation of EREG mRNA expression. Taking into account the IH-induced increase of IL-6 and IL-6-induced upregulation of EREG mRNA in hCASMCs, we hypothesized that elevated IL-6 production due to IH was responsible for the IH-induced increase in EREG mRNA. To determine the direct role of IL-6 in IH-induced increases in EREG mRNA expression, we applied siRNAs for IL-6 and the IL-6 receptor and obtained the result that both siRNAs for IL-6 and IL-6 receptor significantly suppressed the IH-induced increase of EREG mRNA. These results indicated that IL-6 plays a pivotal role in EREG upregulation by IH and consequently DSA-related atherosclerosis.

Supported By: American Diabetes Association (11-13-JF-53 to Y.T) National Institutes of Health

Long Noncoding RNA Zfas1 in Diabetic Cardiomyopathy

BIAO FENG, SHALI CHEN, SUBHRA CHAKRABARTI, London, ON, Canada

Fibrosis is a significant problem in diabetic cardiomyopathy (DCM). Both long noncoding RNAs (lncRNAs) and miRNAs (miR) play important roles in cellular processes. miR-9 targets important extracellular matrix (ECM) protein, such as fibronectin (FN) and collagen (Col), which are upregulated in DCM. The role of ZNF5X1-AS1 (Zfas1), a LncRNA targeting miR-9 in DCM is not clear. We investigated Zfas1 in vitro and in vivo and its regulatory mechanism on ECM protein through miR-9. Microarrays were used to examine LncRNAs and miRNAs expression in ECs exposed to 25 mM glucose (HG) compared to 5 mM glucose and were validated by qPCR. Expression of ECM proteins targeted by miR-9 were examined. Luciferase assay was used to determine the interaction between miR-9 and its target genes. Cardiac tissues from streptozotocin-induced diabetic mice were examined similarly.

The array and qPCR analysis showed glucose-induced upregulation of LncRNA Zfas1 and downregulation of miR-9 in ECs. FN mRNA, Coll1 and 4 mRNA and protein levels were increased in ECs treated with HG. Luciferase assay showed the binding of miR-9 to FN 3’-UTR and miR-9. Zfas1 silencing expression of its target genes expression in HG. Furthermore miR-9 mimics co-transfection with Zfas1 siRNA partially recovered these ECM protein expression. Interestingly, methylation blockade also reduced ECM protein expression. In the hearts of the diabetic animals, Zfas1 expression was increased and miR-9 was decreased and expression of transcripts regulated by miR-9 were increased.

These studies indicate a novel glucose-induced mechanism of increased ECM expression in diabetic cardiomyopathy through miR-9 diabets. Identifying such mechanisms may lead to potential RNA-based treatment for diabetic complications.

Supported By: Heart and Stroke Foundation of Canada

Nrf2 Exaggerates Cardiomyopathy Associated with Type 1 Diabetes in Mice

HUI M. ZANG, WEIWEI WU, LEI QI, CHRISTOPHER BOWEN, TAIXING CUI, HUI M. ZANG, WEIWEI WU, LEI QI, CHRISTOPHER BOWEN, TAIXING CUI, Columbia, SC

Nuclear factor-erythroid factor 2-related factor 2 (Nrf2), a transcription factor for cellular defense against oxidative stress and other insults, has...
been postulated to be an inhibitor of diabetes and diabetic cardiomyopathy. However, this notion has been challenged by the detrimental role of Nrf2 in the pathogenesis of diabetes and diabetic cardiomyopathy. Thus, we investigated the nature of the Nrf2-mediated dichotomy in a mouse model of streptozocin (STZ)-induced type 1 diabetes over a time period of 8 months. We found that global Nrf2 knockdown (Nrf2 KO) increased the death rate in the setting of STZ-induced diabetes, but it partly protected against STZ-induced diabetes and insulin-resistance in both male and female mice. Nrf2 KO hardly affected the onset and the progression of cardiac dysfunction associated with the diabetes by 6 months in both male and female mice; however, it partly prevented the progression of cardiac dysfunction at 9 months. Cardiomyocyte hypertrophy, cardiac fibrosis, and cardiac oxidative stress associated with the diabetes not at 3 months but at 6 and 9 months were inhibited by Nrf2 KO in both male and female mice. In addition, cardiomyocyte- and CD105-ve (CD105) K-D+ (K-D) KO had minimal impact on the blood glucose level, but exaggerated the diabetic cardiomyopathy, which could be attenuated in part by additional Nrf2 KO. At the molecular level, diabetes-induced autophagy impairment turned off Nrf2-operated antioxidant defense while switching on Nrf2-mediated detrimental signaling to cardiomyocytes. Taken together, our findings reveal that Nrf2 is cardioprotective when myocardial autophagy is intact; however, it becomes detrimental to the heart when myocardial autophagy is impaired due to a chronic diabetic setting.

Supported By: National Center for Complementary and Integrative Health; National Institutes of Health

476-P

ROCK2 Regulates the Expression of Cell Adhesion Molecules and Cell-to-Cell Adhesion in Vascular Endothelial Cells

YUSUKE TAKEDA, KIEICHIRO MATOBA, DALJ WOOK NAKANAMI, YOSUKE NAGAI, TOMOYO AKAMINE, SHO ISHIHARA, YASUSHI KANAZAWA, TAMOTSU YOKOTA, KAZUNORI UTUROMIYA, Tokyo, Japan

A pro-inflammatory lipid mediator, lysophosphatidic acid (LPA), is a potent activator of the RhoA/Rho kinase signaling pathway and has been shown to induce the expression of cell adhesion molecules (CAMs). LPA levels are elevated in the circulation of patients with acute coronary syndrome and has also been described inside human atherosclerotic specimens. However, the involvement of Rho-kinase isoforms (i.e., ROCK1, ROCK2) in LPA-mediated expression of CAMs in endothelial cells is not fully understood. In this study, we investigated isoform-specific roles of Rho-kinase in LPA-mediated E-selectin expression using human umbilical vein endothelial cells (HUVECs). Exposure of HUVECs to LPA resulted in an increase of E-selectin expression at both mRNA (real-time PCR) and protein (Western blot) levels. We confirmed increased Rho-kinase activity in the LPA-stimulated cells. Y-27632, a specific Rho-kinase inhibitor, completely abolished E-selectin protein expression, indicating that LPA induces E-selectin expression via Rho-kinase activation. LPA-induced E-selectin gene expression was strongly suppressed by a chemical inhibitor of NF-κB, indicating the contribution of NF-κB transactivation in this pathway. Intriguingly, phosphorylation of NF-κB RelA/p65 was decreased by Rho-kinase inhibition in the LPA-stimulated cells. Furthermore, using isoform specific siRNAs, we found that Rho-kinase isoform ROCK2 is the key mediator of LPA-induced E-selectin expression and cell adhesion between HUVECs and human monocytic cells (THP-1). In the present study, we demonstrate that ROCK2 mediates LPA-induced expression of E-selectin via NF-κB signalling in endothelial cells. ROCK2 could be an important therapeutic target against atherosclerosis.

Gemigliptin Inhibits IL-1β-Induced Endothelial-Mesenchymal Transition via BMP2/Smad/MAPK/Runx2 Pathway

HYUK-SANG KWON, OAKKEE HONG, YANGGYO KANG, HEE SUN KWON, SOON JIB YO, Seoul, Republic of Korea, Bucheon, Republic of Korea, Busan, Republic of Korea

Objective: Endothelial-to-mesenchymal transition (EndMT) contributes to inflammatory conditions inducing conversion of endothelial cells (ECs) into activated fibroblasts, promoting fibrotic diseases. Pro-inflammatory cytokine interleukin (IL)-1β is the most potent inducer of EndMT. We investigated inhibition of IL-1β-induced EndMT by gemigliptin, a DPP-4 inhibitor.

Methods: We exposed human umbilical vein ECs (HUVECs) to 10 ng/ml IL-1β or 20 U/g gemigliptin and analyzed the expression of endothelial, smooth muscle, mesenchymal, and osteoblastic markers, bone morphogenic protein (BMP), Smad, and non-Smad signaling pathway proteins.

Results: Morphological changes showed gemigliptin blocked IL-1β-induced EndMT, upregulated EC markers, and downregulated smooth muscle and mesenchymal markers. IL-1β activation of HUVECs is initiated by the BMP2/Smad and canonical BMP signaling pathways. Gemigliptin inhibited IL-1β induction of BMP2 and 7, activin receptor type 1A, BMP receptor type 1A, and BMP receptor II. Reversal of IL-1β-mediated inhibition of BMP-1/5/8, Smad2, and Smad3 phosphorylation by gemigliptin suggests involvement of the Smad pathway in gemigliptin action. In the canonical BMP pathway, gemigliptin treatment significantly increased the fold that global Nrf2 knockdown (Nrf2 KO) increased the death rate in the setting of STZ-induced diabetes, but it partly protected against STZ-induced diabetes and insulin-resistance in both male and female mice.

Conclusions: We demonstrated a novel protective mechanism of gemigliptin against fibrosis by suppressing IL-1β-induced EndMT.

Supported By: Korea National Research Foundation (2012R1A1A2007988); Yeouido St. Mary’s Hospital

477-P

WITHDRAWN

478-P

Poldip2 Affects Collagen I Accumulation by Regulating the Expression of Zyxin in Vascular Smooth Muscle Cells

MASAKAZU FUJII, NÖRUVI KONDILA, MISATO OKAMOTO, HITOSHI MORIYAMA, YOSHIHIRO OGAWA, KATHY GRIENDLING, FUKUSHIMA, Japan, Atlanta, GA

Objectives: Polymerase delta interacting protein 2 (Poldip2) has previously been implicated in migration, proliferation and extracellular matrix (ECM) production in vascular smooth muscle cells. Therefore, regulation of Poldip2 protein expression is suggested to prevent the development and progression of diabetic macroangiopathy. We recently reported that Poldip2+-/- mouse aortic smooth muscle cells (MASMs) exhibit higher β1-integrin expression and activity of the PI3K/Akt/mTOR signaling pathway, leading to increased ECM protein synthesis. We further investigated the mechanism of Poldip2 in regulating the β1-Integrin expression.

Approach and Results: Cell adhesion and cell signaling, below the focal adhesion, were investigated. Poldip2+/+-/MASMs (HET) showed both quicker cell attachment and detachment than Poldip2+/+MASMs (WT). Paxillin, one of the components of focal adhesion, is expressed in all areas (from front to back) of lamellipodia in WT, on the other hand HET express the Paxillin only front area, which may induce weaker cell adhesion. The mature focal adhesion marker, Zyxin, expression is decreased in HET significantly. Intriguingly, the activity of RhoA is increased in HET and induced MRTF-A translocation from cytosol to nucleus. Conclusions: It is revealed that Poldip2 is positive regulator of Zyxin. HET has weak cell adhesion, and may induce Poldip2+-/MASMs exhibit higher β1-Integrin expression as a compensation against immature focal adhesion. Thus PI3K/Akt/mTOR signaling pathway is activated, leading to increased ECM protein synthesis. Translocation of MRTF-A from cytosol to the nucleus, may contribute to bind to transcriptional factor for Collagen I. This phenomenon is suggested as one more pathway, which Collagen I accumulates in HET. These findings have important implications for atherosclerotic vascular diseases such as diabetic macroangiopathy in which ECM accumulation plays a role.

479-P

Diabetes-Induced Vascular Dysfunction Can Be Attenuated with a Naked G7 Polyamidoamine Dendrimer In Vivo

SAGhir AKHTAR, SINDU CHANDRAKASAR, ANIRUDDHAN N. EL-HASHIM, IBRAHIM BENNET, Dhala, Qatar, Kuwait City, Kuwait, Fatamogusa, Cyprus

Upregulation of epidermal growth factor receptor (EGFR) signaling is involved in development of diabetes-induced vascular dysfunction. Polyamidoamine (PAMAM) dendrimers (branch-like polymers) might be novel inhibitors of EGFR for they inhibit EGFR phosphorylation in vitro. Here, we investigated whether chronic administration of a generation (G) 7 PAMAM dendrimer could have beneficial effects on diabetes-induced vascular dysfunction by inhibiting EGFR signaling in a model of type 1 diabetes. Dendrimer administration (daily ip for up to 4 weeks) to male Wistar rats bearing streptozotocin-induced diabetes dose- and time-dependently inhibited EGFR-ERK1/2-ROCK signaling - a key pathway in the development of diabetic complications - macrovascular - cellular mechanisms of atherogenesis in diabetes

ADA-Supported Research Moderated Poster Discussion
vascular complications. Dendrimer-induced inhibition of EGFR signaling correlated well with a significant correction in hyper-responsiveness of the diabetic mesenteric vascular bed to norepinephrine-a routinely used experimental measure of vascular dysfunction. The dendrimer also inhibited high glucose-induced EGFR-ERK1/2/ROCK signaling in primary vascular smooth muscle cells grown in high (25 mM) glucose. These data show for the first time that a PAMAM dendrimer administered chronically in vivo can lead to inhibition of EGFR-ERK1/2/ROCK signaling and attenuate diabetes-induced vascular dysfunction in an experimental model of diabetes.

Supported By: Kuwait University (MRU/13)

481-P
Canagliflozin Inhibits Human Endothelial Cell Inflammation via the Induction of Heme Oxygenase-1
KEELLY J. FETYON, GHAZALEH BEHNAMMASENH, WILLIAM DURANTE, Colin, A.

Vascular disease is the major cause of mortality in diabetes. Although many factors contribute to diabetes-associated vascular disease, inflammation of endothelial cells (ECs) plays a critical role. Sodium-glucose transporter 2 (SGLT2) inhibitors are recently approved anti-hyperglycemic drugs that cause a significant reduction in cardiovascular events in type 2 diabetic patients, but the mechanisms underlying this protection are not fully known. In the present study, we investigated the effect of SGLT2 inhibitors on the expression of the vasoprotective protein heme oxygenase-1 (HO-1) in human umbilical vein ECs. Treatment of ECs with canagliflozin, dapagliflozin, or empagliflozin stimulated the expression of HO-1 mRNA and protein; however, only clinically achievable concentrations of canagliflozin (3-10μM) increased HO-1 levels. The induction of HO-1 by canagliflozin was associated with an increase in Nrf2 activity and reactive oxygen species (ROS) formation. Canagliflozin also stimulated HO-1 promoter activity, and this was prevented by mutating the antioxidant responsive element or by overexpressing dominant-negative Nrf2. In addition, the canagliflozin-mediated induction of HO-1 was abolished by N-acetyl-L-cysteine or rotenone. Significantly, prior treatment of ECs with canagliflozin inhibited the induction of the adhesion molecules ICAM-1 and VCAM-1 in response to high concentrations of glucose (25 mM) and oxidized low-density lipoprotein (50 mg/L) that mimic the diabetic milieu. Significantly, the anti-inflammatory action of canagliflozin was abrogated by blocking HO-1 activity or expression.

In conclusion, this study demonstrates that canagliflozin stimulates HO-1 gene expression in the vascular endothelium via the ROS-Nrf2 pathway, and that canagliflozin mitigates inflammation in human ECs exposed to a diabetic environment via the induction of HO-1. Thus, canagliflozin may exert some of its vasoprotective effects in diabetes by targeting HO-1.

Supported By: American Diabetes Association (1-17-IBS-290 to W.D.)

482-P
Vasoprotective Effects of Vildagliptin in Mice Is Masked by Metformin—Overlapping Mechanisms Implied
HIDEKI KUSHIMA, YUSUKE MURI, MASAKAZU KOSHIBU, MIUENODI HIROMURA, KYOKO KOHASHI, MICHIGE TERASAKI, TSUTOMU HIRANO, Tokyo, Japan

Preclinical and small clinical studies have demonstrated the direct cardiovascular protective effects of dipeptidyl peptidase 4 inhibitors (DPP-4Is). However, cardiovascular benefits have not been proven in large clinical trials that utilized multiple diabetic agents. We hypothesized that the cardiovascular protective effects of the first-line anti-diabetic agent metformin (Met) affects those of DPP-4Is, so we evaluated the vasoprotective effects of vildagliptin (Vil) in combination with Met in mice.

Methods: We randomly assigned C57BL6 and diabetic db/db mice (8 weeks old) to treatment with vehicle, Vil (3 mg/kg/d), Met (400 mg/kg/d), or the combination of Vil and Met. The mice were subjected to femoral artery wire injury to induce arterial remodeling. Four weeks after the injury, the femoral arteries were harvested. Human umbilical vein endothelial cells (HUVECs) were used in the in vitro experiments. Results: In wild type mice, the biological parameters were similar among the groups. Both Vil and Met treatment reduced neointimal area and vascular cell proliferation to a similar extent (40% reduction) compared to the vehicle, and combining the two drugs did not further reduce those values. Similarly, both Vil and Met treatment reduced neointimal area in db/db mice (50% reduction) without affecting biological parameters, but no additive effect was found. In wild type mice, cotreatment with the nitric oxide (NO) synthase inhibitor completely abolished the vascular effects of both Vil and Met, suggesting that Vil and Met had common mechanisms that are dependent on endothelial NO. In HUVECs, Vil did not directly affect NO production. In contrast, glucagon like peptide (GLP)-1 did stimulate NO production. Met also stimulated NO production. However, the combination of GLP-1 and Met did not increase NO production.

Conclusions: Metformin masks the vasoprotective effects of vildagliptin, possibly because of overlapping mechanisms that are dependent on endothelial NO.

Supported By: Heart and Stroke Foundation of Canada

483-P
Inhibition of NF-κB Pathway with IKK-16 or Linagliptin Attenuates the Cardiac Dysfunction Associated with Polymicrobial Sepsis in Mice with Preexisting Type 2 Diabetes Mellitus (T2DM)
SURA AL ZOUBI, JINMIN CHEN, LIUKAS MARTIN, CATHERINE MURPHY, GARETH S. PURVIS, FAUSTO CHIAZZA, DEBORA COLLOTTA, MASSIMO COLINO, CHRISTOPH THIEMERMANN, London, United Kingdom, Torino, Italy

Introduction: Patients with diabetes are more susceptible to infections and sepsis. Activation of nuclear factor-κB (NF-κB) plays a substantial role in the pathophysiology of sepsis and diabetes. Here we investigate i) the effect of preexisting type 2 diabetes mellitus on cardiac dysfunction associated with sepsis and ii) whether inhibition of NF-κB using IKK-16 or linagliptin attenuates cardiac dysfunction in mice with sepsis and diabetes.

Methods: Ten-week old male C57BL/6 mice received high fat (HFD) or chow diet for 12 weeks, and were then subjected to caecal ligation and puncture (CLP) or sham surgery for 24 hours. At 1 hour after CLP, mice received IKK-16, linagliptin, or vehicle.

Results: Administration of HFD resulted in a significant impairment in glucose tolerance and a small, but significant, reduction in ejection fraction. In wild type mice, cotreatment with the nitric oxide (NO) synthase inhibitor completely abolished the vascular effects of HFD-CLP. Administration of ICAM-1 and VCAM-1 in response to high concentrations of glucose (25 mM) and oxidized low-density lipoprotein (50 mg/L) that mimic the diabetic milieu. Significantly, the anti-inflammatory action of canagliflozin was abrogated by blocking HO-1 activity or expression.

Conclusion: Our results show that HFD results in inflammation and cardiac dysfunction. Moreover, a preexisting diabetic phenotype worsened the pathophysiology of sepsis and diabetes. Here we investigate i) the effect of preexisting type 2 diabetes mellitus on cardiac dysfunction associated with sepsis and ii) whether inhibition of NF-κB using IKK-16 or linagliptin attenuates cardiac dysfunction in mice with preexisting T2DM.

484-P
The Effect of Resveratrol on Reducing Neointimal Growth after Femoral Artery Injury in AMPKα2 Knockout Mice Given High-Fat Diet
LIWEI ZHOU, JUNE GUO, HANGJUN ZHANG, SCOTT HIXMNER, ADRIA GIACCA, Toronto, ON, Canada

The rates of restenosis after percutaneous transluminal angioplasty are higher in diabetic than nondiabetic patients. Insulin is protective against restenosis, but these effects are diminished in the case of insulin resistance, which develops with high fat diet (HFD). Therefore, it makes sense to use an insulin-sensitizing compound which also has vasoprotective effects such as resveratrol. Resveratrol is a phenolic compound found in plant tissues such as the skin of grapes, and has been hypothesized to account for the lower rates of cardiovascular disease among countries with high wine consumption. We have shown that resveratrol decreases neointimal formation in both mouse and rat models of arterial injury, and also that these effects are exerted through eNOS (endothelial nitric oxide synthase). We hypothesized that resveratrol acts though Sirt1, a NAD+-dependent deacetylase, to activate eNOS and decrease neointimal formation, but did not see any difference between neointimal growth of control and Sirt1-/- mice given HFD. AMPK (AMP-activated protein kinase) is an energy sensor which also protects against neointimal hyperplasia in the vasculature via directly activating eNOS and inhibiting the migration of vascular smooth muscle cells. Knocking out the α2 subunit of AMPK in particular has been shown to increase neointimal growth in mouse carotid artery injury to induce arterial remodeling. Four weeks after the injury, the femoral arteries were harvested. Human umbilical vein endothelial cells (HUVECs) were used in the in vitro experiments. Results: In wild type mice, the biological parameters were similar among the groups. Both Vil and Met treatment reduced neointimal area and vascular cell proliferation to a similar extent (40% reduction) compared to that of the vehicle, and combining the two drugs did not further reduce those values. Similarly, both Vil and Met treatment reduced neointimal area in db/db mice (50% reduction) without affecting biological parameters, but no additive effect was found. In wild type mice, cotreatment with the nitric oxide (NO) synthase inhibitor completely abolished the vascular effects of both Vil and Met, suggesting that Vil and Met had common mechanisms that are dependent on endothelial NO. In HUVECs, Vil did not directly affect NO production. In contrast, glucagon like peptide (GLP)-1 did stimulate NO production. Met also stimulated NO production. However, the combination of GLP-1 and Met did not increase NO production.

Conclusions: Metformin masks the vasoprotective effects of vildagliptin, possibly because of overlapping mechanisms that are dependent on endothelial NO.

Supported By: Heart and Stroke Foundation of Canada

Moderated Poster Discussion
ADA-Supported Research
**NMR-Based Lipidomic Analysis of Red Blood Cells Membranes in Type 2 Diabetes**

CHRISTINA KOSTARA, ELENI BARAKTARI, MOSES ELIASF, VASILIEOS TSIMI-HODIMOS, Ioanna GLEAVE

Changes in the composition of red blood cells membranes may lead to an altered blood rheological pattern. Experimental studies suggest that hyperglycemia affects red cell rheology via direct effects on the membrane, including alterations of the lipid membrane bilayer composition and microviscosity and changes in membrane Na+/K+-ATPase function.

We aimed to investigate the 1H NMR-based lipid profile of RBC membranes in type 2 diabetic patients and compare it to that of nondiabetic subjects.

Blood samples from 25 nondiabetic and 15 diabetic individuals were collected after an overnight fast. The groups were matched for age, sex, and conventional lipid parameters. RBCs were lysed and their lipid content was extracted according to a standard procedure. The lipid profile of membranes was recorded on Bruker DRX-500 NMR Spectrometer and analyzed by multivariate data techniques.

The NMR-based lipidomic analysis showed that diabetic patients presented a significantly different lipid profile in RBC membranes compared to that recorded in nondiabetic individuals. RBC membranes from patients with diabetes were characterized by altered fatty acid pattern e.g., higher saturated and lower unsaturated fatty acid levels and lower concentrations of omega-3 fatty acids, mainly docosahexaenoic acid. In addition, lower levels of phosphatidylcholine and phosphatidylethanolamine, and higher levels of omega-3 fatty acids, mainly docosahexaenoic acid. In addition, lower levels of

In conclusion, the lipid composition of RBC membranes in the diabetic state is significantly altered. These disturbances may be involved in the pathogenesis of the microvascular complications of diabetes through the disruption of tissue delivery of oxygen. Additionally, the increased cholesterol content of red cell membranes that reach the lipid core of the atherosclerotic plaques through the vasa vasorum may lead to core expansion, decrease their stability and make them prone to rupture.

**Role of Hyaluronic Acid on Apolipoprotein A1 and HDL-Mediated Cholesterol Efflux in Macrophages**

KOTA MATSUKI, MASATSUNE OSUGI, MARIKO HARADA-SHIBA, Suita, Japan

Diabetic macroangiopathy is characterized by increased arterial stiffness and hyaluronic acid (HA) deposition in the large elastic arteries. It is noteworthy that systemic inhibition of HA synthesis by 4-methylumbelliferyl-

Background: Selective sodium-glucose cotransporter 2 inhibitor (SGLT2i) has become widely used for treatment of diabetes. Recently, EMPA-REG OUTCOME and CANVAS Program showed that SGLT2i reduce cardiovascular events in patients with type 2 diabetes, but the mechanism still remains uncertain. We investigated the mechanisms of vascular protection of Tofogliflozin (Tofo), one of the SGLT2i.

Methods: 1) Streptozotocin (STZ)-diabetic apolipoprotein-E-deficient (Apoe KO) mice were separated into two groups, one group were fed normal chow containing 0.005% Tofo for ad libitum. After 6 weeks, all mice were administered thioglycolate intraperitoneally, and the other were fed normal chow containing 0.005% Tofo for ad libitum. Moreover, the expression levels of inflammatory cytokines in the RBCAs, which are prone to lesion, plaque formation, and rupture. In addition, no plaque was observed in uninjured lesions, while severe plaque formation occurred in injured lesions. In contrast, Lira failed to suppress plaque volume or neointimal thickening in FAs where the VECs were removed (ORO-stained area/vascular wall area: 0.51 ± 0.06 vs. 0.55 ± 0.08, neointimal area/medial area: 2.4 ± 1.2 vs. 2.8 ± 0.7), indicating that Lira cannot suppress atherosclerosis independent of VECs.

Conclusions: Of the multiple actions on various cells, VECs play a central role in the suppression of atherosclerosis mediated by Lira.

Supported by MSD K.K., Novartis Pharma K.K., Novo Nordisk, Sanwa Kagaku Kenkyusho Co., Ltd., Kowa Company, Ltd, Eli Lilly Japan K.K., Mitsubishi Tanabe Pharma Corporation

**Tofogliflozin Suppresses the Progression of Atherosclerosis and Reduces Inflammation in Macrophages of STZ-Diabetic ApoE KO Mice due to Improvement of Glucose Tolerance**

MASAHIKO IWAMOTO, NAOTO KUBOTA, TETSUYA KUBOTA, YOSHITAKA SAKURAI, NOBUHIRO WADA, ISEKI TAKAMOTO, SEIJI SHIODA, TAKASHI KADOWAKI, MASAHIKO IWAMOTO, NAOTO KUBOTA, TETSUYA KUBOTA, YOSHITAKA SAKURA, Suita, Japan

Background: Selective sodium-glucose cotransporter 2 inhibitor (SGLT2i) has become widely used for treatment of diabetes. Recently, EMPA-REG OUTCOME and CANVAS Program showed that SGLT2i reduce cardiovascular events in patients with type 2 diabetes, but the mechanism still remains uncertain. We investigated the mechanisms of vascular protection of Tofogliflozin (Tofo), one of the SGLT2i.

Methods: 1) Streptozotocin (STZ)-diabetic apolipoprotein-E-deficient (Apoe KO) mice were separated into two groups, one group were fed normal chow containing 0.005% Tofo for ad libitum. After 6 weeks, all mice were administered thioglycolate intraperitoneally, and the other were fed normal chow containing 0.005% Tofo for ad libitum. Moreover, the expression levels of inflammatory cytokines in the RBCAs, which are prone to lesion, plaque formation, and rupture. In addition, no plaque was observed in uninjured lesions, while severe plaque formation occurred in injured lesions. In contrast, Lira failed to suppress plaque volume or neointimal thickening in FAs where the VECs were removed (ORO-stained area/vascular wall area: 0.51 ± 0.06 vs. 0.55 ± 0.08, neointimal area/medial area: 2.4 ± 1.2 vs. 2.8 ± 0.7), indicating that Lira cannot suppress atherosclerosis independent of VECs.

Conclusions: Of the multiple actions on various cells, VECs play a central role in the suppression of atherosclerosis mediated by Lira.

Supported by MSD K.K., Novartis Pharma K.K., Novo Nordisk, Sanwa Kagaku Kenkyusho Co., Ltd., Kowa Company, Ltd, Eli Lilly Japan K.K., Mitsubishi Tanabe Pharma Corporation

**Actions of Liraglutide on Vascular Endothelial Cells Play a Central Role in the Suppression of Atherosclerosis in Diabetic Mice**

MUNENORI HIROMURA, YUSAKU MORI, MASAKAZU KOUSHI, HIDEKI KUSHIMA, KYOKI KOSHISHI, MASASHI TERASAKI, TSUTOMU HIRANO, Tokyo, Japan

Background: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have been shown to exert direct anti-atherosclerotic effects through multiple actions on various cells. However, it is unclear which action is crucial. We investigated the role of the anti-atherogenic effects of liraglutide (Lira) on vascular endothelial cells (VECs) in vivo.

Methods: Streptozotocin-induced diabetic apolipoprotein E-null mice (male, 20 weeks) were randomly assigned to treatment with saline or Lira (17 nmol/kg/dl) and underwent femoral artery (FA) wire injury to remove VECs. Thioglycollate-exudated peritoneal macrophages and vascular samples (aorta, FA, and right brachiocephalic artery (RBCA)) were collected 4 weeks after treatment.

Results: In the Lira group, active GLP-1 levels were significantly higher (4.7 ± 1.1 vs. 2.8 ± 0.3 pmol/L) and levels of Hba1c (8.9 ± 0.4% vs. 8.3 ± 0.5%) and total cholesterol (492 ± 8 vs. 457 ± 19 mg/dL) were significantly lower than in controls. Lira significantly reduced the atherosclerotic plaque (oil red O [ORO]-stained area) on the surface of the whole aorta by 36% and the plaque volume and intraplaque macrophage infiltration in the aortic root by 56% and 55%, respectively. Additionally, Lira suppressed the expression of inflammatory cytokines in macrophages by 40-45% (p < 0.05) and the expression of inflammatory cytokines in the RBCAs, which are prone to lesion, plaque formation, and rupture. In addition, no plaque was observed in uninjured lesions, while severe plaque formation occurred in injured lesions. In contrast, Lira failed to suppress plaque volume or neointimal thickening in FAs where the VECs were removed (ORO-stained area/vascular wall area: 0.51 ± 0.06 vs. 0.55 ± 0.08, neointimal area/medial area: 2.4 ± 1.2 vs. 2.8 ± 0.7), indicating that Lira cannot suppress atherosclerosis independent of VECs.

Conclusions: Of the multiple actions on various cells, VECs play a central role in the suppression of atherosclerosis mediated by Lira.

Supported by MSD K.K., Novartis Pharma K.K., Novo Nordisk, Sanwa Kagaku Kenkyusho Co., Ltd., Kowa Company, Ltd, Eli Lilly Japan K.K., Mitsubishi Tanabe Pharma Corporation
Patients with type 2 diabetes mellitus exhibit non-enzymatic glycation of lipoproteins that are considered proatherogenic modification contributing to increased susceptibility of patients with diabetes to atherosclerosis. We postulated that glycated lipoproteins might be associated with vascular outcome. To explore this, we studied the relationship between glycated HDL (gHDL) and glycated LDL (gLDL) with vascular function in African American diabetic patients. Total of 146 diabetic were enrolled over a 6 month period. Levels of plasma gHDL and gLDL were measured by enzyme-linked immunoassay (ELISA). Microvascular function was assessed by vascular reactivity index (VRI). Large artery stiffness was assessed by carotid-femoral pulse wave velocity (PWV). Carotid intima-media thickness (C-IMT) was assessed by B-mode ultrasound image analysis. Mean patient age was 60.0 ± 8.6 years, 64% were female, 80% had hypertension, 50% had dyslipidemia and 15% had chronic kidney disease. Mean HbA1c levels were 8.1 ± 2.2%. Pearson correlation analysis showed no significant correlation between gHDL and gLDL. Multi-regression analysis revealed that gHDL was negatively associated with VRI (β = -0.0.06, p = 0.012, r² = 0.276 for model) in the entire population and in the group of patients with good glycemic control (HbA1c ≤ 7.0; β = -0.0.07, p = 0.031, r² = 0.312 for model). Moreover, gLDL was positively associated with CIMT (β = 0.0.045, p = 0.051; r² = 0.568 for model) after adjustment for other independent variables such as age, gender, stroke, smoking, hypertension, dyslipidemia, HbA1c, diabetes duration, HDLc, and LDLc.

In this cohort, data showed that gHDL was associated with microvascular function, whereas gLDL was mainly correlated with carotid intima media thickness. Further large study is needed to clarify mediating factors of these relationships.

Supported by: New York State Department of Health

**490-P**

**Coronary Microvascular Smooth Muscle Cells Contribute to Heart Failure in Diabetes Mellitus by Increasing Methyglyoxal Flux**

KESHORE BIDASEE, Omaha, NE

Prognosis for patients with type 1 diabetes mellitus (T1DM) who have heart failure is poor because of an incomplete understanding of molecular cues that trigger it and a lack of specific pharmacologic agents/strategies to slow/reverse its development. Supra-physiologic levels of the α-oxoaldehyde methyglyoxal (MG) have emerged as a possible cue. However, its source remains poorly characterized. Here we investigated MG levels and expression of its degrading and synthesizing enzymes glyoxalase-I (Glo-I) and vascular adhesion protein-1 (VAP-1) in ventricular tissues from rats with chronic streptozotocin-induced T1DM. We also used a gene transfer approach to prevent Glo-I downregulation in ventricular tissues to determine if it would be cardio-protective. When compared to controls, hearts of rats with chronic T1DM (10 -12 weeks) had 5-fold higher MG in ventricular tissues, 2.2-fold lower level of Glo-I in ventricular tissues and 2.5-fold higher in coronary microvascular smooth muscle cells (cSMCs). Preventing Glo-I levels downregulation in myocytes and cSMCs of rats by injecting them with an adeno-associated virus contain Glo-I driven by the endothelin promoter one week after the onset of T1DM, attenuated ventricular MG increase, with no effect in blood MG. Increasing Glo-I also blunted VAP-1 upregulation in cSMCs, attenuated microvascular leakage, inflammation, and fibrosis. These data support the notion that an increase in MG arising in part from increased expression of VAP-1 is contributing to HF development in T1DM rats and lowering ventricular MG levels T1DM rats are cardio-protective.

**491-P**

**Renin-Angiotensin System Inhibition Alters Triacylglycerol Metabolism in Diabetic Kidney Disease**

KELLI SAS, JIAHE LIN, VIJIT NAIR, MATTHIAS KRETLZER, FRANK BROSIUS, SUBRAMANIAM PENNATHUR, Ann Arbor, MI; Tucson, AZ

Lipids are essential metabolites with diverse functions impacting physiology. We recently identified several lipidomic abnormalities in diabetic kidney disease (DKD), including remodeling of triacylglycerol (TAG) fatty acid composition to increase availability of long, polyunsaturated TAGs. Using the BKS eNOS-/- db/db diabetic mouse model, we studied the effect of renin-angiotensin system (RAS) inhibition with combination treatment of lisinopril (20 mg/kg/d) and losartan (30 mg/kg/d) for 12 weeks, an intervention which ameliorates DKD in this mouse model without impacting glycemia. We examined the kidney cortical lipidome to identify lipid alterations that may be pathogenic in DKD. As expected, RAS inhibition did not significantly alter glycemic control or total plasma triglycerides or cholesterol, but decreased the 24-hour urine albumin/creatinine ratio (2564 vs. 615 μg/mg creatinine) and decreased the glomerular periodic acid-Schiff stained area by 13% (p=0.05). We performed mass-spectrometry based untargeted lipidomic profiling to quantify 635 lipids across 17 lipid classes in kidney cortex. Lisinopril/losartan treatment remodelled TAG fatty acid composition and increased conversion between TAGs and several glycerophospholipid classes, particularly medium-chain phosphatidylcholines, phosphatidylethanolamines, phosphatidylinositols and cardiolipins (p<0.05). These correlations in lipid levels were associated with changes in corresponding enzymes of lipid metabolism, suggesting increased metabolism of TAGs into glycerophospholipids, which are key components of cell membranes and precursors for signaling molecules. In addition to the known salutary effect of RAS inhibition on DKD, our results suggest a previously unrecognized role of RAS inhibition on kidney complex lipid levels through increased TAG metabolism. These findings raise the possibility that TAG metabolism might be a target for intervention aimed at decreasing DKD progression.

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases; National Institutes of Health
were effectively attenuated by conversion of hyposialylated ANGPTL4 to its secreted hyposialylated ANGPTL4 under high glucose, and these effects the effect of ANGPTL4 on podocyte damage is due to increased podocyte-α1 Integrin/FAK Signaling in Diabetic Nephropathy
HUGO YOO-HSIEN LIN, YUKAY CHEN, YU-HAN CHEN, ALBERT TA, HSIAOCHEN LEE, PING H. WANG, IRVINE, CA
Diabetes increases the risks of ischemia/reperfusion injury, but the etiology is not known. Mitochondrial dysfunction, which can be modulated by AKT1, may play a critical role in nephropathy and subsequent kidney failure. We hypothesized that impaired mitochondrial AKT1 signaling plays a mechanistic role in the pathogenesis of kidney injury. Insulin acutely stimulated AKT1 translocation from the cytosol to mitochondria in renal proximal tubules. In our murine kidney ischemia-reperfusion injury (IRI) model (30 min ischemia followed by reperfusion), serum BUN increased by 2-fold (p=0.001) and creatinine by 5-fold (p=0.038). The Jablonski score of renal tubular injury was significantly elevated after reperfusion (24 hours, p=0.0004; 1 week, p=0.027). Renal fibrosis (% area) in the IRI mice was significantly higher than the sham control mice (p<0.001). Rapid accumulation of phosphorylated AKT1 in the mitochondria at proximal tubules were found 30 minutes (p=0.0303) and 60 minutes (p=0.0173) after IRI. AKT1 translocation to IRI renal tubule mitochondria was confirmed with confocal microscope and western blots of mitochondria proteins. To further dissect the role of mitochondrial AKT1 signaling during IRI in the renal tubules, we have generated novel renal tubule-specific transgenic mice harboring an inducible mitochondria-targeting dominant negative AKT1 (KiDAKT) with cre-lox strategy. After tamoxifen induction, markers for renal tubule injuries (KIM-1, and CD44) were significantly increased in the KiDAKT mice. Histology analysis confirmed renal injury with increased Jablonski score. Therefore, inhibition of mitochondrial AKT1 signaling led to development kidney injury. These findings shed new light into the mechanistic role of mitochondrial AKT1 in nephropathy, and mitochondria signaling may become a novel target to develop new strategies for the prevention and treatment of kidney diseases.

Mechanistic Role of Mitochondrial AKT1 in Kidney Injury and Diabetic Nephropathy

Renal Mitochondrial Oxidative Stress Induced by NAD+-Dependent Sirt3 Inactivation via Overexpression of CD38 (NAD+-ase) in Diabetic Kidney Disease

YOSHIO OGURA, MUNEHIRO KITADA, ITARU MONNO, AI WATANABE, DAISUKE KOYA, IZIKAWA, Japan
Diabetic kidney disease (DKD) is a major cause of end-stage renal disease worldwide. Although the detailed pathogenesis of DKD is not elucidated yet, aging is recognized as one of the risk factors for the development of end-stage renal failure due to chronic kidney disease including DKD. Therefore, investigation of aging-related mechanism would be a novel therapeutic target for DKD. NAD levels decrease during aging. Previous report demonstrated that expression and activity of the CD38 (NADase) increased with aging, and that CD38 is required for the age-related NAD decline and mitochondrial dysfunction via a pathway independent of the expression of Sirt3 activity. However, the role of CD38 in the pathogenesis for DKD has never been investigated. In this study, we evaluated the role of CD38 on the mechanisms of renal mitochondrial oxidative stress which is related to changing Sirt3 activity, in Zucker Diabetic Fatty rats (ZDFrs) and in cultured HK-2 cells under high-glucose condition. At 26 weeks of age, the ZDFrs exhibited elevated HbA1c levels, heavier kidney weight, increased urinary albumin, L-FABP and 8-OHdG excretion, histological tubulo-interstitial fibrosis and tubular cell damage, compared to nondiabetic Zucker Lean rats. Additionally, in renal mitochondria, the NAD+/NADH ratio was reduced, and acetylation levels of mitochondrial antioxidant enzymes, IDH2 and SOD2, which are regulated by Sirt3, were increased in ZDFrs. Similarly, in cultured HK-2 cells under high-glucose condition, CD38 expression was increased, resulting in the reduction of NAD+/NADH ratio and Sirt3 activity, which increased in acetylation levels of IDH2 and SOD2. Administration of the CD38 inhibitor, apigenin, to ZDFrs and HK-2 cells, restored the NAD+/NADH ratio, decreased the levels of IDH2 and SOD2 acetylation. Therefore, restoring Sirt3 activation by suppression of CD38 may be a novel therapeutic target for DKD.

Activation of Brown Adipose Tissue Attenuates Diabetic Nephropathy in Mice

MEPING GUAN, YINGYING CAI, SHAOZHOU ZOU, Guangzhou, China
Brown adipose tissue (BAT) has been regarded as a potential target organ for the treatment of obesity and related metabolic disorders. However, the protective effect of BAT on type 2 diabetic nephropathy (DN) remains unclear. We aimed to test if BAT activation could prevent the development of DN in mice. Type 2 diabetic mice were induced by streptozotocin (STZ) combined with high-fat diet (HFD). CL 316,243, a β3-adrenergic receptor agonist to activate BAT, was administered intraperitoneally (1mg/kg/day) to diabetic mice for 4 weeks. There were no differences in body weight between the groups. Interestingly, the kidney weight and kidney:body weight ratio was significantly higher in the DM-Con mice compared with the Con and DM+CL mice (p < 0.01). Treatment with CL 316,243 significantly reduced blood glucose and improved dyslipidemia. Simultaneously, activation of BAT led to marked decreases in urinary levels of albumin and 8-hydroxy-oxoguanosine
Rho-Kinase Induces CTGF Expression through Actin Dynamics in Mesangial Cells

YUSUKE NAGAI, DALI KAWANAMI, KEICHIRO MATOBA, YUSUKE TAKEDA, TOMOYO AKAMINE, SHO ISHIZAWA, YASUSHI KANAZAWA, TAMOTSU YOKOTA, KAZUNORI UTSUNOMIYA, Tokyo, Japan

Introduction: Transforming growth factor (TGF)-β promotes the development of diabetic nephropathy by enhancing excessive production of extracellular matrix such as connective tissue growth factor (CTGF) in mesangial cells. However, the mechanism by which TGF-β induces CTGF expression has not been elucidated. In this study, we aimed to investigate contribution of small GTPase Rho and Rho-kinase to TGF-β-mediated CTGF expression in mesangial cells.

Methods and Results: Exposure of mouse mesangial cells (MES-13) to TGF-β induced activation of Rho and Rho-kinase. Y-27632, a specific Rho-kinase inhibitor, reduced TGF-β-mediated CTGF protein expression, indicating that TGF-β induces CTGF expression via Rho-kinase activation. Western blot analysis demonstrated that Y-27632 attenuates TGF-β-mediated phosphorylation of Erk1/2 and JNK/SAPK and nuclear translocation of NF-κB. Rho-kinase has been shown to regulate cytoskeleton reorganization. We therefore investigated whether Rho-kinase is involved in actin dynamics-induced NF-κB activation. Immunostaining studies demonstrated that Y-27632 and Cytochalasin D, an inhibitor of actin polymerization, attenuated TGF-β-mediated nuclear translocation of NF-κB, indicating that Rho-kinase-mediated actin reorganization regulates NF-κB activation. Furthermore, siRNA-mediated knockdown of Rho-kinase isoforms demonstrated ROCK2 but not ROCK1 is involved in these observations. In the present study, we demonstrate for the first time that Rho-kinase, especially ROCK2, mediates TGF-β-induced expression of CTGF via phosphorylation of Erk1/2 and JNK/SAPK and subsequent actin reorganization-mediated nuclear translocation of NF-κB in mesangial cells.

Conclusion: Rho-kinase could be an important therapeutic target against diabetic nephropathy.

Sweet-Taste Receptors Mediated ROS-NLRP3 Inflammation Signaling Activation—Implications for Diabetic Nephropathy

LUPING ZHOU, WEI HUANG, YONG XI, CHENLIN GAO, Luhou, China

Previous studies demonstrated that ROS-NLRP3 inflammation signaling activation were involved in the pathogenesis of diabetic nephropathy (DN). But the mechanism by which high glucose prime ROS-NLRP3 inflammation signaling remains debatable. Recent research has shown that taste receptor type 1, member 2 (T1R2) and member 3 (T1R3), form heterodimers to act as sweet taste receptors (STRs), are widely expressed in the extracellular tissues, and emerging evidence suggests that STRs are important sentinels of innate immunity. As a natural ligand for STRs, whether high glucose prime ROS-NLRP3 inflammation signaling via STRs is unclear. Therefore, diabetics melitus (DM) mouse model was induced by streptozotocin (STZ) in vivo, mouse glomerular mesangial cells (GMCs) and human proximal tubular cells were stimulated by elevated concentrations of high glucose (10,20, and 30 mmol/L) or mannitol as the osmotic pressure (OP) control in vitro. STR inhibitor licochalcone A was used as an intervention reagent to evaluated the role and mechanism of the STRs in the pathogenesis of DN. Our results showed that the expression of STRs (T1R2 and T1R3) and associated signaling components (Gαq-gustducin, PLCζ, TRPM5) were obviously down-regulated under the condition of diabetes in vivo and in vitro. Further more, licochalcone A significantly mitigated the production of intracellular ROS and reversed the decrease of Ca2+ and the activation of NLRP3 inflammation signaling in GMCs stimulated by high glucose (p<0.05). These combined results support the hypothesis that high glucose induced ROS-NLRP3 inflammation signaling activation in part via STRs, suggesting that STRs may act as new therapeutic targets of DN.

Backcross db Gene into CD-1 Background Results in Novel Type 2 Diabetic Mouse Model with Progressive Kidney Fibrosis

YUKO MIZUUMA, KYOKO NITTA, SUSUMU TAKAGI, KEIZO KANASAKI, DAISUKE KUWA, Hakoku, Japan

Kidney fibrosis is the final common pathway of progressive kidney disease including diabetic kidney disease (DKD). With the rapid increase of type 2 diabetes, DKD in type 2 diabetic patients has become a serious public health threat around the world. To establish novel therapy to combat DKD, human disease relevant animal model is essential. However, a type 2 diabetic mouse model with presenting progressive kidney fibrosis is not established yet. We have previously reported that kidneys of streptozotocin-induced diabetic CD-1 mice exhibited severe fibrosis compared to other backgrounds of mice associated with the suppression of anti-fibrotic peptide N-acetyl-L-aspartyl-L-lysyl-proline, fibroblast growth factor receptor 1, and their downstream target anti-fibrotic microRNAs (miRNAs) such as miR-29 and miR-let-7. As the type 2 diabetic mice model, leptin receptor deficient mice in BKS background (BKS/ob/ob) are often utilized, the kidney fibrosis in BKS/ob/ob phenotype is minimum. Here we backcrossed db gene into potential fibrotic CD-1 background and found that male CD-1/db/db exhibited severe kidney fibrosis when compared to male BKS/ob/ob. We have already performed the backcrosses for 11 generations. Body weight of CD-1/db/db was comparable but drank up to 3 times more water compared to BKS/ob/ob. Blood glucose levels in CD-1/db/db appeared to be higher when compared to BKS/ob/ob. When evaluated the body weight rate, kidney and heart weighed no significant differences between CD-1/db/db and BKS/ob/ob. CD-1/db/db exhibited severe tubulo-interstitial fibrosis, glomerulosclerosis, and tubular epithelial cells damage. Heart in CD-1/db/db displayed fibrotic change as well.

In conclusion, here we provide novel fibrotic type 2 DKD mouse model. CD-1/db/db could be excellent model to perform experimental therapy for DKD.
ological changes. Kidneys in the Px diabetic rat model displayed hypertrophy of glomeruli, cortex, and medulla 11 weeks post-surgery. Renal fibrosis was significantly increased in Px rats vs. non-diabetic control animals, as determined by quantitative histology following picro-sirius red staining of collagen (total kidney collagen, Px vs. controls, 127 ± 8 mg vs. 39 ± 5 mg, p < 0.001). Plasma urea was increased in Px rats compared to non-diabetic animals (8.3 ± 0.6 vs. 5.5 ± 0.3 mmol/L, p < 0.01). Finally, gene expression of the kidney injury markers NGAL and KIM1 as well as gene expression of pro-fibrotic macrophage markers (mannose receptor, MGL1, and CD163) was increased in Px rat kidneys. Px-UNx rats developed a diabetic phenotype similar to that observed in Px rats. In contrast, a highly increased kidney weight was detected with the more advanced surgical approach. Detailed histological analyses will establish whether glomerular and tubular pathology is exacerbated to a comparable extent.

In conclusion, our data suggest that the Px model develops profound renal hypertrophy and fibrosis, and that renal hypertrophy is exacerbated in the Px-UNx model. Thus, Px alone and Px-UNx in rats may represent novel, strong alternatives to streptozotocin-induced diabetes and genetic models for the study of DN drug candidates.

503-P

PBI-4050 Improves Metabolic Regulation and Diabetic Nephropathy through Reduction of ER Stress, Pro-Inflammatory/Fibrotic Markers, Galectin-3 Expression, and Inflammatory Cell Infiltration in ob/ob Mouse Model

JEAN-CHRISTOPHE SIMARD, MARIE-PIER CLOUTIER, ALEXANDRE LAVERDURE, JONATHAN RICHARD, LIETTE GERVAIS, ALEXANDRA FELTON, BRIGITTE GROUlx, PIERRE LAURIN, MARTIN LEDUC, FRANÇOIS A. LEBLOND, LYNE GAGNON, Laval, QC, Canada

Background: PBI-4050 displays anti-inflammatory/fibrotic properties with metabolic regulation. PBI-4050 has been shown to reduce glycated hemoglobin levels, and different biomarkers related to kidney and heart injury in a phase II open label clinical trial in patients suffering from type 2 diabetes with metabolic syndrome. PBI-4050 has also completed with success an open label phase II clinical trial in patients with idiopathic pulmonary fibrosis (IPF) and in patients with Alström Syndrome. The aim of this study was to investigate the effect of PBI-4050 on diabetic nephropathy in leptin deficient ob/ob mice, a model of type 2 diabetes and metabolic syndrome.

Methods: ob/ob mice were treated with vehicle or PBI-4050 (200 mg/kg, oral once a day) from day 1 to 105. GSTT, triglycerides, adiponectin and serum insulin levels, as well as inflammatory cell infiltration and pro-inflammatory/fibrotic gene expression and histology of kidney and white adipose tissue (WAT) were examined.

Results: PBI-4050 improved glucose metabolism, reduced serum triglycerides and insulin levels, and increased serum adiponectin levels. In kidneys, PBI-4050 reduced ER stress (p-PEK, ATF-6, CHOP and p-IRE1). Furthermore, PBI-4050 reduced κ-SMA, fibronectin and CTGF gene expression. Pro-inflammatory/remodeling markers expression (MRC-1, MCP-1 and MMP-2) were also reduced with PBI-4050 treatment. Moreover, histological analysis revealed that PBI-4050 reduced collagen deposition in glomeruli. Specific immune staining also showed that PBI-4050 significantly reduced galectin-3 expression in kidney and WAT. Finally, PBI-4050 reduced the expression levels of inflammatory cell infiltration markers (Ly6G and F4/80) in kidney.

Conclusions: These results suggest that PBI-4050 is a strong potential candidate for the treatment of metabolic diseases and related diabetic nephropathy.

504-P

Early Growth Response Protein 1 Mediates Long Noncoding RNA Arid2-IR to Promote Extracellular Matrix Production in Diabetic Kidney Disease

YAN-LIN YANG, FANG HUI, MENG XUE, YIJIE JIA, MEINA ZOU, YAO-MING XUE, Guangzhou, China, Shenzhen, China

Background: In order to investigate the mechanism through which Early growth response protein 1 (Egr1) mediates long noncoding RNA Arid2-IR to promote diabetic kidney disease.

Method: In vivo, we induced type 2 diabetes and overexpressed or knocked down Egr1 by rapidly injecting of a large volume of DNA solution through the tail vein. In vitro, we assessed mouse mesangial cells that were stimulated with high glucose conditions and transiently transfected with siRNA and plasmids.

Results: Compared with those in the control group, the expression of Egr1 and Arid2-IR in diabetes mice increased with the up-regulation of Col1a1 and κ-SMA. Arid2-IR expression changes with Egr1 knockdown and overexpression both in vivo and in vitro. Knockdown Arid2-IR in vitro reduced Col1a1 and κ-SMA expression. Overexpressing Egr1 and silencing Arid2-IR reduced Col1a1 and κ-SMA expression.

Conclusion: Egr1 promoted ECM production by up-regulating Arid2-IR. Thus, Arid2-IR may be a new target for treating diabetic kidney disease.

505-P

NADPH Oxidase Nox5 Aggravates Renal Injury in Akita Mouse Model of Diabetic Nephropathy

JAY C. JHA, AOZHI DAI, MARK E. COOPER, RHIAN M. TUDYZ, CHRIS KENNEDY, KARIN JANDELEIT-DAHM, Melbourne, Australia; Glasgow, United Kingdom, Ottawa, ON, Canada

Background: Renal reactive oxygen species (ROS) play an important role in mediating kidney injury in diabetes. Increasing evidence suggests that the pro-oxidant enzyme, Nox5 plays a significant role in human diabetic nephropathy (DN). Nox5 is present in humans and rabbits but not in mice or rats. Thus, there is a paucity of information about Nox5 in conventional animal models of DN. We examined the role of Nox5 in the insulin deficient diabetic Akita mice model using human inducible transgenic mice that express Nox5 selectively in endothelial cells (VEcad+-Nox5+) or in mesangial cells (SM22+-Nox5+). We also examined the endogenous expression of Nox5 in a high fat fed rabbit model of kidney disease.

Methods: At week 10 mice were culled and kidneys were removed for the assessment of structural damage as well as gene and protein expression of markers of inflammation, fibrosis and oxidative stress. Protein expression of Nox5 and its localization in glomerular cells (endothelial and mesangial cells) was examined in transgenic mice by immunostaining. We also examined expression of pro-fibrotic gene in high fat fed rabbits by next generation sequencing (NGS) and RT-PCR.

Results: Expression of Nox5 was confirmed in glomerular endothelial and mesangial cells of transgenic mice. Diabetes induced increase in glomerulosclerosis, gene and protein expression of fibronectin and MCP-1 as well as nitrotyrosine were further increased in both diabetic Nox5 transgenic mice. Moreover, increased expression of Nox5 in high fat fed rabbits vs. normal diet fed rabbits was associated with increased expression of fibronectin, CTGF, collagen IV and VCAM-1 as well as increased mesangial expansion in the kidney.

Conclusions: These findings in both transgenic mice model (endothelial and mesangial cells) suggest that Nox5 plays a significant role in mediating renal injury in diabetes.

Supported By: JDRF; National Health and Medical Research Council of Australia

506-P

miR-877-3p Induces Apoptosis by Targeting BCL2 in Tubular Epithelial Cells

MEINA ZOU, MENG XUE, FANG HUI, YIJIE JIA, YAN-LIN YANG, YAO-MING XUE, Guangzhou, China, Shenzhen, China

Background: Apoptosis of renal tubular epithelial cells plays an important role in the progression of diabetic kidney disease (DKD). Our previous study found that miR-877-3p of urinary exosomes significantly increased
Acute and Chronic Complications

POSTERS

Acute and Chronic Complications

507-P

Early Growth Response 1 (Egr1) Is a Transcriptional Activator of RAAS in Diabetic Kidney Disease
YAO-MING XUE, Guangzhou, China

Background: Egr1 and renin-angiotensin system (RAAS) are involved in DKD, but the relationship between them is unclear.

Methods: Egr1 and RAAS were detected in HFD/STZ-induced mice and HK-2 cells treated with TGF-β1. Then, RAAS expression was detected in HK-2 cells and mice with overexpression and knock-down of Egr1. The direct relationship between Egr1 and RAAS was explored via ChIP assay.

Results: We found increased levels of Egr1 and RAAS in the kidney cortices of diabetes mellitus (DM) mice at 12 w after treatment compared to the renal cortices of 6W. In contrast, BCL2 expression was significantly increased in DM mice compared to control mice only at 12 w after treatment. We also found that miR-877-3p was increased in HG treated HK-2 cells. Overexpression of miR-877-3p in HK-2 cells downregulate the expression of BCL2.

Conclusions: miR-877-3p promotes DKD progression through targeting BCL2.

Figure 1.

508-P

Renin Production and Involvement of β1 Integrin in Blood Pressure Regulation in Diabetic Nephropathy
MASAO TOYODA, NOBUMICHI SAITO, MORITSUGU KIMURA, HITOMI MORIYA, KAIICHIRO SAWADA, MASAFUMI FUKAGAWA, ISEHARA, Japan

Diabetic nephropathy (DN) and hypertension mutually exacerbate each other, but many aspects of the mechanisms of these two pathologies remain unclear. The juxtaglomerular cells (JGC) secrete renin and trigger the renin-angiotensin-aldosterone system involved in blood pressure regulation. Integrins (lfts) are cell surface proteins that interact with the extracellular matrix and transduce intracellular signals in response to extracellular stimuli. There are several phosphorylation sites in the β1 chain, and phosphorylation plays an important role in the cell-binding ability and intracellular signaling functions of lfts. Our previous immunohistochemical analysis of renal tissue sections of diabetic patients showed that β1 Itg, a cellular matrix adhesion factor, undergoes JGC-specific phosphorylation. To characterize the relationship between the phosphorylated β1 (pβ1) Itg and renin expression in DN, the following studies were conducted in rats with streptozotocin (STZ)-induced diabetes.

Immunohistochemical analysis of the prepared sections showed JGC-specific phosphorylation of β1 Itg in the kidneys of diabetic rats. Immunofluorescent staining of these kidney tissue specimens confirmed the coexpression of pβ1 Itg and renin in JGC. The mRNA levels of pβ1 Itg decreased continuously with time in diabetic rats after the onset of diabetes, till month 2. However, the mRNA levels of pβ1 Itg increased subsequently, but ultimately showed recovery to the baseline level. In contrast, the renin mRNA ratio exhibited an inverse correlation with pβ1 Itg. Quantification by image analysis of confocal laser microscopic images confirmed the negative correlation between pβ1 Itg and renin.

Our results showed a negative correlation between pβ1 Itg and renin expression in renal JGC, suggesting a link between β1 Itg and the regulatory system that controls renin production and secretion.

Figure 2.

509-P

Klotho Prevents Epithelial-Mesenchymal Transition through Egr-1 Down-Regulation in Diabetic Kidney Disease
YANG LI, MENG XUE, FANG HU, YUE JIA, YAN-LIN YANG, YAO-MING XUE, GUANGZHOU, China, Shenzhen, China

Background: As a key event leading to tubulointerstitial fibrosis in diabetic kidney disease (DKD), epithelial-mesenchymal transition (EMT) has drawn...
increasing attention from researchers. Klotho attenuates renal fibrosis in part by inhibiting ERK1/2 signaling in DKD. Early growth response factor 1 (Egr-1), activated mainly by ERK1/2, has been shown to play an important role in EMT. However, whether Klotho prevents EMT by inhibiting ERK1/2-dependent Egr-1 expression in DKD is unclear. The aim of this study was to investigate whether Klotho prevents EMT through Egr-1 down-regulation by inhibiting the ERK1/2 signaling pathway in DKD.

Methods: Male C57BL/6J mice fed an HFD for 4 weeks received 120 mg/kg STZ. Klotho and Egr-1 expression was detected in the renal cortices of these mice upon their sacrifice at 12 and 12 w after STZ treatment. In vitro studies, we incubated HK2 cells under high-glucose (HG) or TGF-β1 conditions to mimic DKD. We then transfected the cells with an Egr-1-containing plasmid, Egr-1 siRNA, a Klotho-containing plasmid or Klotho siRNA. Klotho, tions to mimic DKD. We then transfected the cells with an Egr-1-containing plasmid, Egr-1 siRNA, a Klotho-containing plasmid or Klotho siRNA. Klotho, Egr-1, E-cadherin, α-smooth muscle actin (α-SMA), fibronectin (FN), ERK1/2 and p-ERK1/2 were determined.

Results: Klotho expression was significantly decreased in the renal cortices of diabetes mellitus (DM) mice compared to control mice at 6 w and was even more significantly decreased at 12 w. In contrast, Egr-1 expression was significantly increased in DM mice compared to control mice only at 12 w. We also found that Klotho overexpression down-regulated Egr-1 expression and the (p-ERK1/2)/ERK1/2 ratio in HG- or TGFβ1-treated HK2 cells. Conversely, Klotho silencing up-regulated Egr-1 expression and the (p-ERK1/2)/ERK1/2 ratio. Moreover, the effects of si-Klotho were abolished by the ERK1/2 inhibitor PD98059.

Conclusions: Klotho prevents EMT during DKD progression, an effect that has been partially attributed to Egr-1 down-regulation mediated by ERK1/2 signaling pathway inhibition.

Supported By: National Natural Science Foundation of China (8157024); Natural Science Foundation of Guangdong Province, China (2014A030312009)

510-P Klotho Prevented Epithelial-to-Mesenchymal Transition in High-Fat Diet/Streptozotocin-Induced Mice by Targeting NfkB/Mirna-21/Smad7 Signaling Pathway

MENG XUE, FANG HU, XIANG LI, YIJIE JIA, YAO-MING XUE, Shenzhen, China

Klotho is an antiaging hormone present in the kidney that protect renal via attenuating the nuclear factor-kB (NFkB) p65 activity. And in kidney epithelium miRNAs become active in response to injury. But little is known regarding to the role of Klotho on miRNAs in the pathogenesis of diabetic nephropathy (DN). In this study, we found that the expression of Klotho was reduced with upregulation of miR-21 and key parameters of DN in HFD/STZ-induced diabetic mice. Klotho-treatment reduced p65 nuclear expression in association with modulation of miR-21/Smad7 and amelioration of fibrosis. Furthermore, we found that Klotho expression was decreased in high glucose induced HK2 at both mRNA and protein, accompanied by the significantly increased miR-21 expression. NF-kB was demonstrated to regulate miR-21 expression by directly binding to its promoter. Additionally, exogenous addition of Klotho or inhibition of NF-κB restrained the activity of miR-21/Smad7 signaling pathways, which suppressed fibrosis in high glucose cultured HK2. This study provides a new basis to elucidate the protection mechanism of anti-aging protein Klotho in diabetic kidney. We firstly found that Klotho treatment could delay the fibrosis progression of diabetic nephropathy in type 2 diabetic mice via inhibition of NF-kB/miR-21/Smad7 signaling cascade pathways.

Supported By: National Natural Science Foundation of China (8157024)

511-P Empagliflozin and Linagliptin Alleviate Glomerular Changes in a Model of Diabetic Nephropathy

ANTON I. KORBUT, VADIM KLIMONTOV, IULIIA TASKAEVA, NATALIYA P. BGA-

Korbut, Novosibirsk, Russia

The Aim: To assess the effects of SGLT2 inhibitor empagliflozin, DPP-4 inhibitor linagliptin, and their combination on structural changes in kidneys in a model of type 2 diabetic nephropathy. Eight-week-old male db/db diabetic mice (BKS.Cg-Dock7m+/+lepr/Vj) were treated with empagliflozin (10 mg/kg), linagliptin (10 mg/kg), combination of both agents, or placebo for 8 weeks. Nondiabetic heterozygous db/+ mice were used as control. Renal structural changes were analyzed quantitatively from the light and electron microscopic images. Both empagliflozin and linagliptin, either alone or in combination, attenuated mesangial expansion estimated by mesangial volume (p=0.008 for empagliflozin, p=0.03 for linagliptin and combination). The width of glomerular basement membrane was diminished in all treated groups (all p<0.01). In diabetic mice, podocytopeny was manifested by the foot process effacement (p=0.03). Under treatment, the number of podocyte foot processes increased (p=0.003 for linagliptin, p=0.03 for empagliflozin and combination) and the width of podocyte foot processes decreased in all treated groups (p=0.003 for empagliflozin and linagliptin, p=0.01) for combination. The number of endothelial fenestras in glomerular capillaries was increased by the treatment (all p<0.01). The interaction between empagliflozin and linagliptin was significant for the number and width of podocyte foot processes, and the number of endothelial fenestras (all p<0.01). The effects of both agents on structural changes were not associated with hypoglycemic activity. The obtained results demonstrate that empagliflozin and linagliptin ameliorate renal fibrosis and podocyte injury in a model of type 2 diabetic nephropathy.

Supported By: Institute of Cytology and Genetics, Siberian Branch, Russian Academy of Sciences (RFMEFI1914000505, RFMEFI214100010)

512-P Changes of Plasma and Urine hsa-miR-223-3p Was Correlated with the Severity in Different Stages of Diabetes Kidney Disease of Type 2 Diabetes Patients in China

JUNYI HE, RONG LI, LAN LI, YANAN WU, QIUPING YANG, LIHUA ZHANG, Kun-ming, China

We have previously shown that hsa-miR-223-3p can be as a candidate novel biomarker performing important roles in Diabtes Kidney Disease (DKD) disease process, resulted from co-expression analysis from miRNA (Agilent chips) and IncRNAs (Affymetrix HsTA2.0 chips) in plasma. This study involved into 30 patients with type 2 diabetes mellitus (T2DM) and normal control (n=28). Then we divided these diabetes patients into Normoalbuminuric groups (DM) (n=30), Microalbuminuric group (Micro-DKD) (n=30) and Macroalbuminuric group (Macro-DKD) (n=30), according to urinary albumin to creatinine ratio (ACR) levels (<30mg/g, 30-300mg/g, >300mg/g). The clinical data and biochemical indexes of all the subjects were collected. Real-time qPCR to detect miR-223-3p expression of plasma and urine were reported and compared by using the one-way ANOVA. Statistical analysis was performed using SPSS version 23 software. Receiver operating characterstic (ROC) curves and the area under the ROC curve (AUC) were used to estimate the diagnostic value of the candidate miRPs. Compared with controls, the expression of miR-223-3p in plasma were decreased significantly from DM, Micro-DKD to Macro-DKD groups (p<0.001), and the decline was gradually accompanied with the progression of DKD (p<0.001). Same decline pattern was observed in urine expression among four groups, however discrimination was not significant due to the limited patients enrollment in the study. The ROC curve showed that the level of miR-223-3p in plasma can be distinguished among Micro-DKD, Macro-DKD with controls (AUC = 0.750, 95% CI = 0.569-0.923, p = 0.008; AUC = 0.986, 95% CI = 0.992-1.000, p = 0.000). Therefore, plasma hsa-miR-223-3p is a novel biomarker for the severity in Different Stages of DKD in China.

Supported By: Yunnan Provincial Science and Technology Department (2017FE88-042)

513-P TRIM29 is a New Gene That Regulates IRS-1 to Induce Insulin Resistance in Diabetic

SAMY L. HABIIB, San Antonio, TX

Insulin resistance is a major risk for development of type 2 diabetes. Sev-eral genes involved in regulation of insulin receptor substrate 1 (IRS1) and lead to chronic diabetes. Our RNA sequence data from kidney of diabetic mice show a new candidate gene involved in the regulation of IRS1. New candidate gene, Tripartite motif protein 29 (TRIM29), acts as an E3 ligase targetting insulin receptor (IR) and insulin receptor substrate 1 (IRS1) for ubiquitin-dependent degradation, resulting in insulin resistance. RNA seq data show that TRIM29 is higher 2.5 and 3.6 fold in kidney cortex of diabetic mice (db/db) at age of 10 and 12 months compared to wild type mice, respectively. Mouse renal proximal tubular epithelial cells treated with high glucose (25mM) for 48 hours showed significant increased in TRIM29 and decreased in IRS-1 compared to cells grown in normal glucose (5mM). Pre-transfected cells with siRNA against TRIM29 resulted in significant increased IRS-1 and cell proliferative marker, cyclin D1 expression. Downregulation of tuberin by siRNA significantly decreased TRIM29 expression and increased cyclin D1 expression. In addition, downregulation of AMPK by DN-AMPK and com-pound C resulted in decreased TRIM29 expression. Both emtpy decreased TRIM29 compared to cells transfected with control-siRNA. Kidney cortex of db/db mice and WT mice at age 10 and 12 months were analyzed by Western blot showed that TRIM29 is significantly increased and IRS-1 decreased compared to wild type mice. Increase TRIM29 in kidney diabetic mice was associated with increased in...
COMPLICATIONS—NEPHROPATHY—CLINICAL AND TRANSLATIONAL RESEARCH

514-P

A Low-Protein Calorie-Restricted Diet Attenuates Renal Injury and Facilitates Podocyte Autophagy in Type 2 Diabetic Rats

GUOFANG CHEN, YAN GENG, CHAO LIU, NANJING, China, Jiangsu, China

Purpose: Caloric restriction has been shown to exert a renoprotective effect in diabetic rats. Dietary protein restriction slows the progression of nephropathy in diabetic patients. We explored whether a low-protein caloric-restricted (LPCR) diet reduces renal injury and whether the renoprotective effect of LPCR diet is related to the activation of podocyte autophagy.

Methods: The type 2 diabetic rat model was induced by a combination of high fat diet and low dose streptozotocin injection. The diabetic rats were randomly divided into 3 groups, normal protein (NP, 20% protein) group, low protein (LP, 8% protein) group and LPCR (8% protein, 30% restriction) group. Nondiabetic rats were used as normal control (NC). After 4 weeks of dietary intervention, urine albumin-to-creatinine ratio, creatinine clearance, serum creatinine, and kidney-to-body weight ratio, renal histologies, podocyte density, autophagy activity in glomeruli as well as glomerular basement membrane thickness and autophagic vacuoles in podocytes under electron microscopy were estimated.

Results: The LPCR-diet treated diabetic rats exhibited reduced body weight, serum triglycerides, and fasting blood glucose levels, as well as improved insulin resistance compared with NP-diet treated diabetic rats. LPCR diet attenuated renal injury, including podocyte injury, in type 2 diabetic rats. The reduced number of autophagic vacuoles in podocytes and insufficient podocyte autophagy in type 2 diabetic rats were reversed by LPCR diet.

Conclusions: The findings suggest that a LPCR diet can ameliorate renal injury in type 2 diabetic rats, which maybe linked to the activation of podocyte autophagy.

Supported By: National Natural Science Foundation of China (81471010)

515-P

Identifying a New Pathway to Regulate Autophagy in HK2 Cells

EURO YAMADA, SHUICHI OKADA, MASANOBU YAMADA, Maebashi, Japan

Diabetic nephropathy (DN) is one of the major diabetic complications, the leading cause of the end stage renal disease (ESRD). Recently autophagy, which is also implicated in diabetes and insulin resistance, was shown to regulate DN. Recently, we demonstrated that Fyn functions as a muscle mass regulator by suppressing macroautophagy through a STAT3-mediated inhibition of the Vps34/Beclin1/ATG14 complex 1 but it is still not known whether Fyn regulates autophagy in kidney and function as a pathway-genesis of DN. To investigate this, siRNA mediating knockdown of Fyn in HK2 cells as an in vitro cell model of renal proximal tubular epithelial cells was performed and demonstrating not only decreased p62 expression but also increased LC3-1/2 ratio implicating increased autophagy. To further investigate autophagic flow we utilized ammonium chloride and leupeptin to inhibit the autophagic flow and consistently found that expression of LC3-2 was increased. Phospho-proteomic analysis were performed in vivo and revealed that Fyn phosphorylates Transglutaminase 2 (Tgm2), a known autophagic direct Fyn substrate, we incubated human purified GST-Tgm2 protein with purified Fyn-CA. In the presence of ATP, Fyn was observed to robustly phosphorylate the Tgm2. Interestingly, Fyn-dependent phosphorylation of Tgm2 was abolished when Y389 and Y617 in Tgm2 was mutated (Tgm2-Y389/617F). suggesting that these sites were specific and unique for Fyn kinase. SiRNA inhibits Tgm2-WT decreased autophagic flow demonstrating Tgm2 could regulate autophagy in the renal tubulus. Taken together, these data suggest that Fyn phosphorylates Tgm2 on Y389 and Y617 and regulates autophagy in the renal tubulus implicating a pathogenesis of DN.

Supported By: Japan Society for the Promotion of Science

516-P

Unbiased Stereological Quantification of Key Features of Diabetic Nephropathy

TANJA X. PEDERSSEN, THEA T. JOHANSEN, LISBETH N. FINK, NIELS VRANG, THOMAS SEDERH, Harsholm, Denmark

Diabetic nephropathy (DN) is a serious long-term complication of diabetes. There is no curative treatment of DN, and the lack of knowledge about mechanisms leading to DN hampers the development of efficient therapies. To facilitate drug development, the ability to quantify key histopathological changes in animal models of human DN is essential. In order to develop a more precise determination of translatability nephrographic changes, we used novel and refined image analyses and stereological quantification of key features of DN in a model approach combining genetic diabetes (db/db mice) with uninephrectomy (UNx). UNx or sham-operation was performed in db/db or db/+ male and female mice (n=8-16 mice per group) and the study was terminated 10 or 16 weeks after surgery. Diabetes development was similar in sham and UNx/db mice. Compared to sham-operation, UNx increased average kidney weight in db/db females both after 10 (43%) and 16 weeks (48%). Blood urea nitrogen (BUN) was increased in UNx vs. sham-operated animals 4 weeks post-surgery, but not at termination. Notably, kidney fibrosis was increased in UNx and sham db/db vs. sham db/+ females (16 weeks; mg total collagen, 12.7 ± 1.3 and 10.7 ± 1.8, respectively, vs. 5.7 ± 0.8, p<0.05). Urinary albumin was progressively increased in all db/db groups with significantly lower variance in UNx db/db females than sham (F-test, p=0.02), permitting smaller group sizes in preclinical studies. Unbiased stereological quantification is ongoing to establish volume of glomeruli and number of podocytes. Glomerular collagen is quantified by double-fluorescence imaging concomitantly detecting podocin and collagen.

In conclusion, renal hypertrophy and raised plasma BUN suggest increased pressure on the remaining kidney in UNx mice, leading to fibrosis and decreased kidney function. The thorough quantification of translatable features of DN in the db/db UNx model may provide refinement of this model enabling improved pharmacological testing of compounds targeting DN.

COMPLICATIONS—NEPHROPATHY—CLINICAL AND TRANSLATIONAL RESEARCH

Moderated Poster Discussion: Clinical and Translational Studies in Diabetic Kidney Disease (Posters: 517-P to 522-P), see page 29.
Apolipoprotein C3 and Cardiovascular Disease in Patients with Type 1 Diabetes and Diabetic Nephropathy

LARS STECHEMESSER, CAROL FORSBLOM, RAIMUND WEITGASSER, PER-HENRIK GROOP, Salzburg, Austria, Helsinki, Finland

Background and Aims: Apolipoprotein C3 (ApoC3) is a key regulator of triglyceride metabolism via its inhibitory effects on lipolysis and hepatic remnant uptake. Emerging evidence indicates that ApoC3 is an independent risk factor for cardiovascular events. The fact that glucose and insulin regulates ApoC3 expression raises the role of ApoC3 and cardiovascular risk in diabetes. We, therefore, investigated ApoC3 and its association with cardiovascular disease (CVD) in patients with and without diabetic nephropathy.

Methods: This cross-sectional and prospective analysis was part of the prospective, ongoing Finnish Diabetic Nephropathy (FinnDiane) Study. Between 1994 and 2015 data were obtained from 3926 type 1 diabetes (T1D) patients at more than 80 hospitals or health centers across Finland. ApoC3 levels were explored by groups of albuminuria, CKD stages, presence of CVD as well as prediction of CVD and death. Survival curves were calculated by Cox regression analysis.

Results: At baseline, normo-, micro- and macroalbuminuria were present in 71.7%, 13.8% and 14.5% of the population (n=3926, females 48%, age 37±12 years, diabetes duration 23±13 years, HbA1c 8.4±1.5%). CKD stage 3-5 was diagnosed in 14.3%. Coronary heart disease or stroke (CVD) were present in 5.5% at baseline, while 16.3% developed CVD during 15-year follow-up. Compared to normal albuminuria ApoC3 was elevated in the presence of micro- (p=0.013) or macroalbuminuria (p<0.001). Increasing ApoC3 levels were observed alongside progression of CKD stage (p<0.001). Notably, higher baseline ApoC3 correlated with presence of CVD at baseline, development of CVD during follow-up and death. Differences in survival of those with the highest quartile of ApoC3 were independent of eGFR, triglycerides or HbA1c.

Conclusions: Baseline ApoC3 levels were elevated in T1D patients with micro- and macroalbuminuria, with impaired renal function, and with CVD. ApoC3 also predicted the development of CVD and death during follow-up.

Circulating MicroRNAs Associated with Incident End-Stage Renal Disease in Chinese with Type 2 Diabetes

BAOQI FAN, HEUNG MAN LEE, CADMON K.P. LIM, RICHARD CHOI, JULIANA C. CHAN, ANDREA LUK, RONALD C. MA, BAOQI FAN, HEUNG MAN LEE, CADMON K.P. LIM, RICHARD CHOY, JULIANA C.

Objectives: We aimed to identify novel serum micro(mi)RNAs associated with incident end-stage renal disease (ESRD) in Chinese with type 2 diabetes.

Methods: We conducted a nested case-control study in patients with type 2 diabetes enrolled in the Hong Kong Diabetes Registry between 1995 and 2007. Cases were patients who were free from ESRD at enrolment but developed renal endpoint as defined as eGFR < 15 ml/min/1.73m2 or dialysis during follow-up until 2015. Controls were patients who had normal renal function at both baseline and during observation period. MicroRNAs were extracted from stored serum collected at baseline. Discovery cohort included 22 cases and 21 controls and miRNAs were screened by Agilent microRNA microarray. Validation cohort included 361 ESRD cases and 241 T2D controls and miRNAs were quantitated using qRT-PCR. Two spike-in miRNAs were used to control for efficiency in RNA extraction and reverse transcription. Batch difference was adjusted by a positive RNA control.

Results: In the discovery analysis, miR-X and miR-Y were elevated with respective fold-change of 5.97 and 4.43 in patients with incident ESRD compared to those without renal events on follow-up. Pathway analysis revealed that the two miRNAs may involve in signaling transduction, adrenergic signaling, or relate to peroxisome. Increased levels of miR-X and miR-Y were also detected in the validation cohort. Using binary logistic regression adjusted for age, sex and disease duration, doubling of miR-X and miR-Y were associated with 14.2% and 26.3% higher odds of progressing to ESRD, respectively. The association remained significant for miR-Y when further adjusted for metabolic indices, baseline albuminuria and eGFR.

Conclusions: Baseline serum levels of miR-X and miR-Y are independently associated with higher risk of incident ESRD. These results indicate the potential of circulating miRNAs to serve as prognostic indicators for disease progression.

Supported By: Chinese University of Hong Kong (T12-402/13N)

Elevated Serum Neutrophil Gelatinase-Associated Lipocalin (NGAL) and Intra renal Hemodynamic Dysfunction in Type 1 Diabetes (T1D)

PETTER BJURNSTAD, JANET K. SNELL-BERGEON, JULIE A. LOVSHIN, SUNITA K. SINGH, LEIF ERIK LOVLOM, JOSEPHINE M. TSE, ANDREJ ORSZAG, YULIYA LTYTVN, MICHAEL H. BRENT, NARINDER PAUL, ALANNA WEISMAN, HILLARY A. KEENAN, LESLIE CHAM, VERA BRIL, BRUCE A. PERKINS, DAVID CHERNEY, Aurora, CO, Toronto ON, Canada Londres ON, Canada Boston MA

Little is known about how tubular injury relates to intrarenal hemodynamic dysfunction in T1D. We sought to define the relationships between serum NGAL, a marker of tubular injury, and intrarenal hemodynamic function (glomerular filtration rate [GFR], effective renal plasma flow [ERPF], renal vascular resistance [RVR]) in T1D adults. The cohort consisted of patients with longstanding T1D (>50 years duration); 44 Diabetic Nephropathy (DN) Resistors (eGFR>60 mL/min/1.73m2 and <30mg/day urine albumin excretion) and 22 with DN. GFR [ml/min/1.73m2] and ERPF [ml/min/1.73m2] were measured, and afferent arteriolar resistance [R(A)], efferent arteriolar resistance [R(E)], and RVR were derived from Gomez equations. Serum NGAL was measured using immunoassay kits from MSD. Serum NGAL was higher in DN vs. DN Resistors (median, IQR: 224[136, 355] vs. 138[106, 191]ng/mL, p=.001). Serum NGAL inversely correlated with GFR (r=-0.33, p=.006), ERPF (r=-0.34, p=.006) and positively with R(E) (r=0.26, p=.03) and RVR (r=0.31, p=.01). Subjects in the highest NGAL tertile had lower GFR and ERPF, and greater R(E) and RVR vs. those in the lowest tertile (Figure).

Differences remained significant after adjusting for age, sex, HbA1c, SBP and LDL. DN Resistors had significantly lower serum NGAL vs. those with DN. Elevated NGAL is related to intrarenal hemodynamic dysfunction and afferent vasocostruction in longstanding T1D.

Figure.

Advanced Glycation End Products (AGEs)—Role in Development and Progression of Kidney Disease in Type 1 Diabetes in DCCT/EDIC

PAUL J. BEISSWENGER, IONUT BEBU, SCOTT HOWELL, JOHN LACHIN, and Progression of Kidney Disease in Type 1 Diabetes in DCCT/EDIC

Introduction: Early diagnostic measures that predict development of complications in individuals with type 1 diabetes would be clinically relevant. Our goal was to determine if glycative and oxidative stress biomarker levels are independent risk factors in the development of advanced diabetic kidney disease (DKD) prior to detection of overt disease in the DCCT and follow-up EDIC.

Methods: Using a case-cohort design, we measured plasma and urine levels of 5 Advanced Glycation (AGEs) and 2 oxidation end-products by LC-MS/MS.
Acute and Chronic Complications

Toronto in eGFR levels with exenatide (LSMD +0.21 [-0.27, 0.70] mL/min.1.73m², and disease characteristics). Time to event models, with and without covariate adjustment (demographics model. Effects on renal composites were estimated with interval censored least squares mean difference (LSMD) eGFR (95% confidence interval [95% from a prespecified analysis plan.

Renal Outcomes in the EXenatide Study of Cardiovascular Event Lowering (EXSCEL)


Background: EXSCEL was a multinational, randomized, blinded, placebo-controlled, pragmatic CV outcome trial of once-weekly exenatide on the renal outcomes in patients with type 2 diabetes. Other renal outcomes were numerically but not statistically improved with exenatide.

Table.

<table>
<thead>
<tr>
<th></th>
<th>Exenatide</th>
<th>Placato</th>
</tr>
</thead>
<tbody>
<tr>
<td># with event, % (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence/100 pers.</td>
<td></td>
<td></td>
</tr>
<tr>
<td># without event, % (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence/100 pers.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal composite 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>296/1456</td>
<td>3.2</td>
<td>273/458</td>
</tr>
<tr>
<td>Adjusted HR*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40% eGFR decline</td>
<td>279</td>
<td>266</td>
</tr>
<tr>
<td>Renal replacement</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Renal death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Renal composite 2</td>
<td>396/1256</td>
<td>1.9</td>
</tr>
<tr>
<td>Adjusted HR*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40% eGFR decline</td>
<td>236</td>
<td>228</td>
</tr>
</tbody>
</table>

40% eGFR decline

Renal replacement

Renal death

New macroalbuminuria

1 Adjusted for age, sex, ethnicity, race, region, duration of diabetes, prior history of CV event, insulin use, baseline HbA1c, eGFR, and DMR.

Results: Intention-to-treat analyses showed no significant difference in eGFR levels with exenatide compared to placebo (p=0.39). New macroalbuminuria occurred in 2.2% and 2.5% of the exenatide and placebo groups (p=0.19). There was a 15% lower renal composite 2 adjusted risk with exenatide (p=0.027) (Table).

Conclusions: A composite of 40% eGFR decline, renal replacement, renal death or new macroalbuminuria was significantly reduced in an adjusted analysis by the addition of exenatide in a broad range of people with type 2 diabetes. Other renal outcomes were numerically but not statistically improved with exenatide.
525-P

Urinary NGAL and KIM-1 Are Significantly Elevated in Young Adults (YA) with Type 1 (T1D) and Type 2 (T2D) Diabetes

NICOLE M. SHEANON, AMY K. MOTTL, RALPH DAGOSTINO, JR., CYNTHIA SUERKEN, MARYAM AFKARIAN, DANIEL J. PETTITT, SHARON SAYDAH, LAWRENCE M. SUERKEN, MARYAM AFKARIAN, DANNA DABLEA, GIUSEPPINA IMPERATORE, NICHOLE M. SHEANON, AMY K. MOTTL, RALPH DAGOSTINO, JR., CYNTHIA SUERKEN, MARYAM AFKARIAN, DANNA DABLEA, GIUSEPPINA IMPERATORE

Support by: National Institutes of Health; Centers for Disease Control and Prevention

Figure. Time to incident or worsening nephropathy adjusted for time-dependent covariates

<table>
<thead>
<tr>
<th>Type 1 (T1D)</th>
<th>Type 2 (T2D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial value</td>
<td>Final value</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>Microalbuminuria</td>
</tr>
<tr>
<td>0.01</td>
<td>0.05</td>
</tr>
<tr>
<td>0.05</td>
<td>0.10</td>
</tr>
<tr>
<td>0.10</td>
<td>0.20</td>
</tr>
<tr>
<td>0.20</td>
<td>0.40</td>
</tr>
<tr>
<td>0.40</td>
<td>0.80</td>
</tr>
<tr>
<td>0.80</td>
<td>1.60</td>
</tr>
</tbody>
</table>

526-P

Factors Related to the High Prevalence of Diabetic Kidney Disease in Ecuador—Update for Health Policy Makers

MARIANA E. GUADALUPE, GRACIELA B. ALVAREZ CONDO, FANNY E. VERA LORENTI, BETTY J. PIZAMINO GOMEZ, EDGAR I. RODAS NEIRA, DOLORES VERON, ALICIA G. CERCAIDO, GUILLERMO A. VILLEGAS, ALDA TUFRO, DELMA VELRAG, Milagro Ecuador Cordoba Agginiting Sucos, My New Haven, CT

Type 2 diabetes mellitus (T2DM) and diabetic kidney disease (DKD) are prevalent diseases in South America. Identification of factors associated with DKD is key to design appropriate regional health policies. We characterized DKD in 1963 adults (99% Confidence level, 1.4% margin of error) recruited from the general population of the Ecuadorian coast between 2014 and 2017 (46±14 years of age, 64% of them were women). Framed in our prospective, observational and cross-sectional study (NCT02237352) we evaluated demographic data, personal and family history, BMI, blood pressure (BP), plasma glucose (PG), HbA1c, creatinine (cr) and microalbuminuria (µAlb).

T2DM was defined as people with clinical diagnosis of T2DM, being on insulin or oral hypoglycemic treatment, fasting PG ≥126 mg/dl, random glucose ≥200 mg/dl and HbA1c ≥6.5%.

Results: Our study shows that the prevalence of DKD in the Ecuadorian coast was 9.3% (95% CI, 8%-11%) with 19.5% of the persons not knowing their T2DM status. The factors significantly different comparing DKD vs. non-DKD subjects (p<0.05) were: Female 71.4% (CI 95%, 64%-78%) vs. 57.4% (95% CI, 61%-66%); age 58±9 vs. 45±14 years; BMI 29.5±4.9 vs. 27.7±5.3 Kg/m²; systolic BP 133.5±20.9 vs. 119.4±16.8 mmHg; diastolic BP 82.9±13.4 vs. 75.4±12 mmHg; PG 197.3±103.6 vs. 98.4±41.5 mg/dl; HbA1c 8.8±2.6 vs. 7.5±1.3%; personal history of gestational diabetes (GD) 7.3% (95% CI, 3%-14%) vs. 2.4% (95% CI, 2%-4%) and overweight newborn children (OBNC) 30.9% (95% CI, 23%-41%) vs. 14.7% (95% CI, 13%-17%).

Conclusion: Female gender, age, BMI, BP, PG, HbA1c, history of ONBC and GD are all factors related to DKD in the Ecuadorian coast that should be considered to design meaningful health policies, to address the current high prevalence of DKD. The amount of people unknown their diagnosis of T2DM among folks with DKD suggests emphasizing the screening of T2DM.


527-P

Presence of Carotid Artery Plaque Is Associated with Rapid Renal Function Decline in Patients with Type 2 Diabetes and Normal Baseline Renal Function

DA HEA SE, SO HUN KIM, SEONG HEE AHN, SEOKBING HONG, MOON SUK NAM, JEONG-TAEK WOO, SE HYUN BAIK, Kwan woo LEE, YOUNG SOO KIM, YOUNG SOO PARK, Incheon, Republic of Korea, Seoul, Republic of Korea, Suwon, Republic of Korea, Seongnam, Republic of Korea, Champaign, Illinois, Republic of Korea

Background: Recent clinical evidences indicate that early rapid renal function decline is closely associated with the development of diabetic kidney disease. We have investigated the incidence and baseline clinical predictors of rapid renal function decline in patients with type 2 diabetes and normal baseline renal function.

Methods: A total of 967 type 2 diabetic patients from the Korean National Diabetes Program (KNDP), a prospective, multicenter, observational cohort study, with serial GFR measurement for 5 years and normal renal function were included for the analysis. Rapid renal function decline was defined as an eGFR decline >3.3% per year. Carotid ultrasonography was used to assess carotid intima-media thickness (IMT) and the presence of plaque.

Results: The mean age was 53.7 years with body mass index of 25.4 kg/m². Rapid renal function decline developed in 158 participants (16.3%) and average GFR decline was -5.2 ± 1.9% /year in rapid decliners and -0.4 ± 1.3% /year in non-decliners. There were no differences in the presence of albuminuria or retinopathy between the rapid decliners and non-decliners at baseline. Multivariable logistic regression analyses revealed that female sex (odds ratio (OR) 4.80 (95% CI 2.69-8.56), p<0.0001), higher urine albumin/creatinine ratio (OR 1.28 (1.03-1.55), p=0.028), presence of carotid artery plaque (OR 2.58 (1.47-4.55), p<0.001), and previous history of hypertension (OR 1.93 (1.03-3.44), p=0.025) and CVD (OR 2.53 (1.24-5.15), p=0.011) were the independent clinical predictors for rapid renal function decline.

Conclusions: Our study suggests the need for close monitoring of renal function and early intensive management in patients with type 2 diabetes and carotid atherosclerosis.

Supported by: National Institutes of Health; Centers for Disease Control and Prevention

ADA-Supported Research  Moderated Poster Discussion
Levels of Connective Tissue Growth Factor (CTGF) Predict Development of Kidney Dysfunction in Type 2 Diabetes—The VADT Study

KELLY J. HUNT, MIYAN R. JAFFA, SARA M. GARRETT, DEIRDRE K. LUTTRELL, KENNETH E. LIPSUN, MARIA F. LÓPEZ-VIRELLA, LOUIS M. LUTTRELL, AYAD A. JAFFA, VADT INVESTIGATORS, Charleston, SC; Beirut Lebanon, San Francisco, CA

Connective tissue growth factor (CTGF) is a member of the CCN family of matricellular proteins that has been implicated in the inflammatory process, response to injury and wound healing. An emerging role of CTGF is that of a profibrotic factor implicated in the development of kidney disease. Our objective was to determine the role of CTGF as a predictor of macroalbuminuria (AER >300µg/mg twice) and chronic kidney disease (CKD) stage 3 (GFR <60ml/min twice) and stage 4 (GFR <30ml/min once or twice) in the VADT cohort. Levels of CTGF were measured in 952 VADT patients, a median of 1.9 years after entry into the study. Participants were followed for a median of 3.9 years for renal outcomes. CTGF categories were defined as below the detectable limit (i.e., referent, 54.5%), lower half of detectable values (i.e., 22.8%) and upper half of detectable values (22.7%). Odds ratios (ORs) for kidney endpoints in relation to CTGF categories were calculated by logistic regression. Even with adjustment for baseline ACR levels, individuals in the highest compared to lowest CTGF category were at higher risk of macroalbuminuria [OR=3.21 (95% CI: 1.37, 7.53)]. In contrast, CTGF was predictive of incident stage 3 and stage 4 CKD only when baseline GFR levels were not adjusted for. Our study indicates that high levels of CTGF are associated with and predict future kidney dysfunction in patients with type 2 diabetes.

<table>
<thead>
<tr>
<th>Endpoint/CTGF Category</th>
<th>n*</th>
<th>Model 1**</th>
<th>Model 2***</th>
</tr>
</thead>
<tbody>
<tr>
<td>MA (ACR &gt;30µg/mg twice)</td>
<td>780</td>
<td>35</td>
<td>1.00</td>
</tr>
<tr>
<td>CTGF Below detectable limit</td>
<td>780</td>
<td>35</td>
<td>1.00</td>
</tr>
<tr>
<td>CTGF 7.8-13.4 µg/ml</td>
<td>1.34 (0.50, 3.62)</td>
<td>0.94 (0.32, 2.73)</td>
<td></td>
</tr>
<tr>
<td>CTGF 13.4-26.3 µg/ml</td>
<td>4.50 (2.03, 10.10)</td>
<td>3.21 (1.37, 7.53)</td>
<td></td>
</tr>
<tr>
<td>CKD Stage 3 (GFR &lt;60ml/min twice)</td>
<td>712</td>
<td>136</td>
<td>1.00</td>
</tr>
<tr>
<td>CTGF Below detectable limit</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>CTGF 7.8-13.4 µg/ml</td>
<td>1.22 (0.75, 1.97)</td>
<td>0.92 (0.54, 1.56)</td>
<td></td>
</tr>
<tr>
<td>CTGF 13.4-26.3 µg/ml</td>
<td>2.00 (1.21, 3.32)</td>
<td>1.57 (0.89, 2.76)</td>
<td></td>
</tr>
<tr>
<td>CKD Stage 4 (GFR &lt;30ml/min once)</td>
<td>927</td>
<td>33</td>
<td>1.00</td>
</tr>
<tr>
<td>CTGF Below detectable limit</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>CTGF 7.8-13.4 µg/ml</td>
<td>1.40 (0.51, 3.83)</td>
<td>0.98 (0.35, 2.78)</td>
<td></td>
</tr>
<tr>
<td>CTGF 13.4-26.3 µg/ml</td>
<td>3.97 (1.76, 8.95)</td>
<td>2.15 (0.89, 5.21)</td>
<td></td>
</tr>
<tr>
<td>CKD Stage 5 (GFR &lt;15ml/min once)</td>
<td>893</td>
<td>14</td>
<td>1.00</td>
</tr>
<tr>
<td>CTGF Below detectable limit</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>CTGF 7.8-13.4 µg/ml</td>
<td>1.98 (0.43, 9.16)</td>
<td>1.07 (0.22, 5.30)</td>
<td></td>
</tr>
<tr>
<td>CTGF 13.4-26.3 µg/ml</td>
<td>5.19 (1.49, 18.5)</td>
<td>1.82 (0.43, 7.69)</td>
<td></td>
</tr>
</tbody>
</table>

Supported By: National Institutes of Health/National Heart, Lung, and Blood Institute (5R1H0177192-09).
Methods: Medline, Embase, Web of Science and Cochrane Central Register of Controlled Trials were searched from 1991 to September 2017. Randomized controlled trials (RCTs) were selected to evaluate the impact of TZDs on urinary albumin, protein excretion, eGFR or Scr in diabetic patients. Weighted (WMDs) and standardized mean differences (SMDs) were used for changes in urine albumin or protein excretion, eGFR and Scr between theTZDs and control groups.

Results: 26 RCTs (9 with rosiglitazone and 17 with pioglitazone) involving 8129 patients with type 2 diabetes were included in this review. Meta-analysis of RCTs showed that in patients with baseline normo- and/or microalbuminuria, the WMD of proportional changes between the TZDs and control groups in urinary albumin excretion was -64.77% (95% CI, -75.60 to -53.94) and the WMD of changes in albumin-creatinine ratio was -24.94% (95% CI, -38.83 to -11.05). Overall, in participants with normo- and/or microalbuminuria, TZDs treatment was associated with a significant decrease in urinary albumin excretion (SMD, -0.91 units of standard deviation [SD]; 95% CI, -1.19 to -0.64). Similarly, TZDs were associated with a significant decrease in urinary protein excretion in patients with macroalbuminuria (SMD, -1.06 units of SD; 95% CI, -1.86 to -0.27). However, TZDs treatment couldn’t effectively improve eGFR or the level of Scr in diabetic patients whether with microalbuminuria or macroalbuminuria.

Conclusions: Treatment with TZDs can benefit patients with early diabetic nephropathy in absence of renal dysfunction.

Supported By: National Natural Science Foundation of China (81600756, 81070822, 81370938); Jiangsu Higher Education Institutions (PAPD JX10231801)

Elevated Baseline Glomerular Filtration Rate Is Associated with a More Rapid Decline in Chinese Patients with Type 2 Diabetes with Normoalbuminuria

531-P

JING WAN, HAIBING CHEN, Shanghai, China

Aims: To investigate the association between estimated baseline glomerular filtration rate (eGFR) and renal function decline in Chinese patients with type 2 diabetes.

Main Methods: A longitudinal study was performed on 368 Chinese patients with type 2 diabetes whose estimated GFR (eGFR) was determined at baseline with a 3.12-year follow-up. The patients were divided into three groups according to baseline eGFR (mL/min/1.73 m²): G1 (eGFR > 120), G2 (60 ≤ eGFR < 120), G3 (60 ≤ eGFR < 90).

The association between baseline eGFR and the renal function decline rate was assessed using binary logistic regression. Decliners were defined as a negative change ≥ -3.3% per year.

Key Findings: Among G1 patients, the decliners were younger, had a higher baseline eGFR, shorter duration of diabetes, and lower diastolic blood pressure, compared with non-decliners. The G1 eGFR slope (% per year) was significantly higher than that in G2 and G3 patients. The percentage of decliners among G1 patients was significantly higher than that among G2 and G3 patients. Baseline eGFR group, HbA1c, hypertension history, age of decliners among G1 patients was significantly higher than that among G2 and G3 patients. Baseline eGFR (≥ 120 mL/min/1.73 m²) was an important predictor for diabetic nephropathy (DN). Adipocyte fatty acid-binding protein (A-FABP) is a major cytoplasmic protein in adipocytes and is closely associated with metabolic syndrome and type 2 diabetes. We aim to investigate the role of adipokines including A-FABP and inflammatory cytokines in the development of rapid renal function decline in type 2 diabetes and normal renal function.

Methods: A total of 456 subjects with type 2 diabetes with normal renal function were recruited from an outpatient clinic at the Diabetes Center of Inha University Hospital and were followed up for 6 years with serial glomerular filtration rate (GFR) measurements. The serum levels of tumor necrosis factor (TNF)-a, and interleukin (IL)-6, high molecular weight (HMW) adiponectin, endogenous secretory receptor for advanced glycation end products (esRAGE), A-FABP and pentraxin-related protein (PTX3) were measured at baseline. Rapid renal function decline was defined as an eGFR decline ≥ 3.3% per year.

Results: During follow-up, 120 participants (26.3%) developed rapid renal function decline and mean annual eGFR decline was -5.4 ± 2.7% and the -0.6 ± 2.4% in decliners and non-decliners, respectively. Median A-FABP levels were significantly higher in patients with rapid decliners than in non-decliners (19.1 vs. 18.6 ng/ml, p = 0.011). No significant difference of three cytokines levels were observed between groups. Each log unit increase of A-FABP was associated with greater risk of rapid renal function decline (odds ratio [OR] = 3.60; 95% confidence interval [CI] 1.95-6.66; p < 0.001) after adjustments for sex, BMI, A1C, GFR, hypertension, presence of carotid artery plaque and urine albumin creatinine ratio.

Conclusions: High plasma A-FABP was an independent risk factor for rapid renal function decline in type 2 diabetes and normal renal function.

533-P

Serum Adipocyte Fatty Acid-Binding Protein Levels Are Linked to Rapid Renal Function Decline in Patients with Type 2 Diabetes and Normal Renal Function

DA HEA SEI, SO HUN KIM, SEONG HEE AHN, SEONGBIN HONG, MOONSUK NAM, Inchon, Republic of Korea

Background: Rapid renal function decline has been recognized as an important predictor for diabetic nephropathy (DN). Adipocyte fatty acid-binding protein (A-FABP) is a major cytoplasmic protein in adipocytes and is closely associated with metabolic syndrome and type 2 diabetes. We aim to investigate the role of adipokines including A-FABP and inflammatory cytokines in the development of rapid renal function decline in type 2 diabetes and normal renal function.

Methods: A total of 456 subjects with type 2 diabetes with normal renal function were recruited from an outpatient clinic at the Diabetes Center of Inha University Hospital and were followed up for 6 years with serial glomerular filtration rate (GFR) measurements. The serum levels of tumor necrosis factor (TNF)-a, and interleukin (IL)-6, high molecular weight (HMW) adiponectin, endogenous secretory receptor for advanced glycation end products (esRAGE), A-FABP and pentraxin-related protein (PTX3) were measured at baseline. Rapid renal function decline was defined as an eGFR decline ≥ 3.3% per year.

Results: During follow-up, 120 participants (26.3%) developed rapid renal function decline and mean annual eGFR decline was -5.4 ± 2.7% and the -0.6 ± 2.4% in decliners and non-decliners, respectively. Median A-FABP levels were significantly higher in patients with rapid decliners than in non-decliners (19.1 vs. 18.6 ng/ml, p = 0.011). No significant difference of three cytokines levels were observed between groups. Each log unit increase of A-FABP was associated with greater risk of rapid renal function decline (odds ratio [OR] = 3.60; 95% confidence interval [CI] 1.95-6.66; p < 0.001) after adjustments for sex, BMI, A1C, GFR, hypertension, presence of carotid artery plaque and urine albumin creatinine ratio.

Conclusions: High plasma A-FABP was an independent risk factor for rapid renal function decline in type 2 diabetes and normal renal function.

534-P

Structure Equation Modeling Analysis of Risk Factors and the Pathway Associated with Chronic Kidney Disease in Patients with Type 2 Diabetes

TAO CHUN LEE, FU-MEI CHUNG, Pingtung, Taiwan, Kaohsiung, Taiwan

Background: Diabetes mellitus is the most common cause of chronic kidney disease (CKD), however, the inter-relationships and pathogenetic mechanisms among risk factors are still largely unknown. Structural equation models (SEM) was applied to test a hypothesis model of causal pathways related to CKD in patients with type 2 diabetes mellitus (T2DM).

Methods: A total of 3,395 subjects with T2DM were enrolled in this study. A hypothesized SEM was applied to assess associations between demographic data, diabetic self-management behaviors, diabetes control,
Glycemic Fluctuation and the Risk of Hypoglycemia Unawareness Associated with Hemodialysis in Type 2 Diabetic HD Failure

Akinori Hayashi, Akari Mimasu, Sayuri Kawase, Tatsuguji Masaki, Sonomi Yoshino, Akifumi Ogawa, Koji Takanosu, Masayoshi Shichiri, Sagamihara, Japan

Despite the high-risk of asymptomatic hypoglycemia associated with hemodialysis (HD) using glucose-free dialysate, presence of dialysate glucose is believed to prevent intradialytic hypoglycemia. However, exact glycemic fluctuation profiles and frequency of asymptomatic hypoglycemia during HD remain unappreciated. Using continuous glucose monitoring, we evaluated glycemic excursions in 63 type 2 diabetic HD patients (44 male, HbA1c 6.4±1.2%) treated with a dialysate containing either 100, 125 or 150 mg/dL glucose. Average sensor glucose level (SGL) at start of HD after 7.2±5.0 U bolus insulin and breakfast was 187±56.2 mg/dL. SGL showed gradual and sustained decrease during HD irrespective of the dialysate glucose levels (Figure). SGL nadir reached below the dialysate glucose levels in 23 of 37 patients treated with dialysate containing 100 mg/dL glucose, in 14 of 17 patients with 125 mg/dL and in all 9 patients with 150 mg/dL. Fourteen of all 63 patients (22%) presented with HD-related hypoglycemia as defined by SGL <36 mg/dL during HD or immediately after HD up until the next meal. All hypoglycemic episodes revealed asymptomatic.

In conclusion, type 2 diabetic HD patients present a high-risk of HD-related hypoglycemia unawareness despite the use of dialysate containing 100-150 mg/dL glucose. SGL may fall well below the dialysate glucose level toward the end of HD.

Plasma Uric Acid (PUA), Renal Hemodynamic Function, and Arterial Stiffness at the Extremes of T1D Duration—Adolescents vs. Adults with T1D for ≥50 Years

Yuliy Lytvyn, Petter Bjornstad, Julie A. Lovshin, Genevieve Boulet, Mohammed Farooqi, Vesta S. La, Josephine M. Tse, Leslie Cham, Leif Ney, Toronto, ON, Canada, Aurora, CO

Results: Of 250,742 patients identified, the median age was 61 years, 58% were male, 73% were Caucasian and 87% had hypertension. Proportions of patients using angiotensin II receptor blockers (ARB) or angiotensin-converting enzyme inhibitors (ACEI) was lower in CKD stages 4 and 5 (54 and 52%, respectively) than in stages 1-3 (66-70%). The use of beta blockers (32-52%), calcium channel blockers (27-41%) and diuretics (37-54%) tended to increase from CKD stages 1 to 4 and decrease in stage 5. Antidiabetic drugs were prescribed to 65.7% of patients and their use decreased with increasing CKD stage. Of the 21% of patients who progressed within a year to a more severe CKD stage, the highest proportion advanced from stage 4 to 5 (42%). The most common clinical events were diabetic retinopathy, heart failure and acute kidney injury reported in 27%, 22% and 22% of patients, respectively. Overall, 4.6% died with a median time from index to death of 12.3 months. The annual healthcare costs of $46,028 per person included $5,103 and $36,325 for pharmacy and medical costs, respectively.

Conclusions: The treatment of T2DM patients with CKD was mostly in line with current guideline recommendations. However, only up to 70% of patients used ARB and ACE, the first line treatments. In addition, 21% of patients progressed to a more severe CKD stage. These findings suggest a need for new treatment options in this population.
Factors Responsible for Progression of Microalbuminuria in Japanese Patients with Type 2 Diabetes—Retrospective Analysis
SODAI KUBOTA, HITOSHI KUWATA, DAISUKE YABE, KENTA MIYAMOTO, YOSHI-YUKI HAMAMOTO, TAKESHI KURUSE, YUTAKA SEINO, Osaka, Japan, Kobe, Kobe University, Kobe, Japan

Aim: This study was designed to investigate factors associated with progression or remission of microalbuminuria (MA) in Japanese type 2 diabetes (T2D).

Methods: Patients with MA, defined as urinary albumin/cre ratio (UACR) ≥30 mg/gCre, were retrospectively screened from medical records of 65,323 patients who visited Kansai Electric Power Hospital between 2006 and 2009 (baseline period); and their status of MA was re-evaluated between 2014 and 2017 (evaluation period) using mean values of multiple measurements of UACR or urinary protein/cre ratio (UPCR). Data were analyzed using γ² test, ANOVA and logistic regression analysis.

Result: T2D patients with MA identified in the baseline period (n=155) had 3 different outcomes in the evaluation period: Group A (n=26), UACR <30 mg/gCre; group B (n=106; UACR 30-299 mg/gCre) and group C (n=23, UACR >300 mg/gCre or UPCR >500 mg/gCre). Mean and standard deviation (SD) of HbA1c during the observation period differ significantly among different groups in the evaluation period (Table 1), despite of the similar baseline age, BMI, T2D duration and Hba1c. Mean and SD HbA1c also associated with MA (Mean OR 2.18, 95% CI: 1.23-3.88). SD OR 9.91, 95% CI: 2.57-38.2).

Conclusion: Sustained glycemic control is the critical to prevent MA progression in Japanese T2D.

Table 1. Glycemic Control and Use of Drugs during the Observation Period.

<table>
<thead>
<tr>
<th>Group</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n(M/F)</td>
<td>26(20/6)</td>
<td>106(76/30)</td>
<td>23(16/7)</td>
<td></td>
</tr>
<tr>
<td>Mean HbA1c (%)</td>
<td>7.44±0.11</td>
<td>7.39±0.05</td>
<td>7.80±0.13</td>
<td>0.014</td>
</tr>
<tr>
<td>Standard deviation of HbA1c during total observation period (%)</td>
<td>0.51±0.05</td>
<td>0.58±0.02</td>
<td>0.77±0.07</td>
<td>0.013</td>
</tr>
</tbody>
</table>

| Antihypertensive drug use (%) | 73.1 | 70.8 | 95.7 | 0.043 |
| Lipid-lowering drug use (%) | 73.1 | 78.3 | 69.6 | n.s. |
| Antiplatelet drug use (%) | 19.2 | 32.1 | 29.6 | n.s. |
**COMPLICATIONS—Nephropathy—Clinical and Translational Research**

### 542-P

**Wider Peripheral Retinal Vessel Predicts Renal Dysfunction in Adolescents with Type 1 Diabetes**

VALILIMAYI VELAYUTHAM, MARIA E. CRAIG, GERALD LIW, TIEN Y. WONG, AULDA JENKINS, KIM C. DONAHUJE, Campbelltown, Australia, WEost, Australia, Sydney, Australia, Singapore, Singapore.

Objective: The renal and retinal vasculature shares similar pathophysiological features. Retinal vascular changes, even without typical retinopathy, can predict microvascular disease in type 1 diabetes (T1D). We hypothesise that peripheral retinal vessels are wider and predict incident renal dysfunction in adolescents with T1D.

Research Design and Methods: In this longitudinal study of 441 retinopathy-free and normoalbuminuric adolescents with T1D, retinal photographs were measured by computer software (Singapore I Vessel Assessment) with vessel calibers summarized in the standard "central zone" [Central Retinal Artery and venular equivalents (CRAE and CRVE respectively)] and "extended zone" [Mean width of arterioles and venules (MWa and MWv)]. Retinal vascular geometry including length/diameter ratio (LDR) and simple tortuosity (ST) was quantified. Generalised estimation equation was used to explore associations between vessel calibres, LDR, ST and incident renal dysfunction. Incident renal dysfunction was defined as Albumin excretion rate (AER) >7.5 µg/min, with results expressed as odds ratio (OR) and 95% CI.

Results: Mean ± SD age was 14.1±1.5 year, median diabetes duration 4.8 years [IQR 3.3, 7.5], A1C 8.4 ± 1.3% [IFCC 68 ± 42.4 mmol/mol]. Incident renal dysfunction occurred in 186/441 (42%) over a median 4 year follow-up. Wider MWa and MWv (4th vs. 1st quartile), higher LDR (4th vs. 1st-3rd quartile) and lower ST (1st vs. 2nd-4th quartile) were associated with renal dysfunction: MWa OR 2.0 (1.2, 3.5); MWv 2.2 (1.3, 3.8); LDRa 1.5 (1.0, 2.1); STa 1.5 (1.1, 1.8) after adjusting for covariates (AIC, diabetes duration, gender, height and blood pressure). Central vessels were not related to renal dysfunction: CRAE: 0.9 (0.5, 1.0); CRVE: 1.3 (0.8, 2.1); all p<0.05.

Conclusions: We speculate that small vessel dislilation and tortuosity are modulators of diabetic renal disease.

### 543-P

**Superior Glycaemic Control Effects with Dulaglutide (Dula), a Once-Weekly Glucagon-Like Peptide Receptor-Antagonist (GLP-1RA), to Liraglutide (Lira) in Diabetic Hemodialysis Patients Assessed by Continuous Glucose Monitoring (CGM)**

SATOSHI FUKUNOSHI, MASATOSHI HAYASHIDA, KENJI SAWASE, TAKASHI SATOSHI FUNAKOSHI, MASATOSHI HAYASHIDA, KENJI SAWASE, JUNICHIRO HARADA, NAGASAKI, Japan, Tokyo, Japan.

Objective: Dulaglutide (Dula) is a novel, long-acting glucagon-like peptide receptor antagonist (GLP-1RA) used in the treatment of T2D patients with or without renal impairment. In this study we compared by using CGM, once-daily Lira and once-weekly Dula, each combined with various doses of insulindegludec (IDeg).

Methods: Eighteen adult HD patients with T2D (men/women, 11/7) who had been treated with once-daily Lira (0.6-0.9 mg) combined with daily IDeg (5-26 units) (Lira + IDeg) were switched to once-weekly Dula 0.75 mg combined with daily IDeg (Dula + IDeg). The dose of IDeg stayed the same in each patient, and all patients were monitored for PG control by CGM, and study endpoints or feasibility are assessed in clinical trials of patients with diabetes and CKD.

Results: A significant reduction was observed in MAGE with Dula + IDeg 4 weeks after switching to Lira + IDeg both in on-HD days (122.3±38.3 mg/dL vs. 68.7±2.2 mg/dL, p<0.001) and off-HD days (88.9±24.1 mg/dL vs. 42.8±20.3 mg/dL, p=0.001). No episode of hypoglycemia, and 4 out of 18 patients reported mild gastrointestinal adverse events with Dula treatment, but were thought to be related.

Conclusions: Thus, Dula appears to be potentially superior to Lira in reducing PG fluctuations in HD patients with T2D receiving IDeg.
DKA and ESRD were older, presented with more severe hyperglycemia and had longer LOS; however, response to therapy and mortality was similar to patients without ESRD.

Table.

<table>
<thead>
<tr>
<th></th>
<th>DKA with ESRD n: 65 (9.5%)</th>
<th>DKA without ESRD n: 676 (90.5%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>57.4 ± 15.2</td>
<td>43.7 ± 17.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>41 (63)</td>
<td>306 (50)</td>
<td>0.04</td>
</tr>
<tr>
<td>BMI, mean (kg/m²)</td>
<td>29.6 ± 9.2</td>
<td>27.2 ± 7.5</td>
<td>0.033</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>9.9 ± 2.6</td>
<td>11.7 ± 2.8</td>
<td>0.003</td>
</tr>
<tr>
<td>BG, mg/dl</td>
<td>753.6 ± 441</td>
<td>585 ± 250</td>
<td>0.003</td>
</tr>
<tr>
<td>Admission potassium, mEq/L</td>
<td>22.9 ± 7</td>
<td>22.8 ± 6</td>
<td>0.95</td>
</tr>
<tr>
<td>Bicarbonate, mmol/L</td>
<td>12.0 ± 4</td>
<td>11.5 ± 3.9</td>
<td>0.26</td>
</tr>
<tr>
<td>Effective Osm, mOsm/kg</td>
<td>303.9 ± 23</td>
<td>298.7 ± 17</td>
<td>0.02</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>131.0 ± 7</td>
<td>132.1 ± 6</td>
<td>0.12</td>
</tr>
<tr>
<td>Beta-hydroxybutyrate, mmol/L</td>
<td>5.0 ± 3.1</td>
<td>6.3 ± 2.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Admission potassium, mEq/L</td>
<td>5.7 ± 1.4</td>
<td>5.1 ± 1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to BG &lt; 250 mg/dl, minutes</td>
<td>372.1 ± 279</td>
<td>415 ± 228</td>
<td>0.79</td>
</tr>
<tr>
<td>Hospital mortality, n (%)</td>
<td>2 (3)</td>
<td>11 (2)</td>
<td>0.36</td>
</tr>
<tr>
<td>LOS, median days (Q1, Q3)</td>
<td>8 (5, 16)</td>
<td>3 (2, 5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypoglycemia &lt;70 mg/dl, n (%)</td>
<td>10 (15)</td>
<td>77 (13)</td>
<td>0.56</td>
</tr>
<tr>
<td>Hypokalemia &lt; 3.0 mEq/L, n (%)</td>
<td>16 (25)</td>
<td>126 (20)</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Acknowledgments: This study was supported in part by research grants from the National Institute of Diabetes and Digestive and Kidney Diseases (DK017979, DK080096). The authors wish to thank Dr. Sarah L. Duvall for her assistance with statistical analysis.

**Moderated Poster Discussion: Latest Breakthroughs in the Clinical and Basic Science of Diabetic Neuropathy (Posters 547-P to 552-P), see page 25.**

**Genetically Reduced Chondroitin Sulfate Prevents the Progression of Diabetic Neuropathy**

HAIJIME ISHIYUGU, TAKASHI USHIKI, ASAMI KAWASAKI, KADRI CHO, MASAYOSHI MASUKI, KAZUNORI SANGO, MICHIIHIRO IGARASHI, HIROHITO SONE, NIGATA, Japan, Tokyo, Japan

Background: The extracellular matrix is associated with the pathophysiology of diabetic complications; however, the role of chondroitin sulfate (CS) remains unclear. To clarify the effects of CS on diabetic neuropathy (DN), we assessed the effect of genetically reducing CS in mice through disruption of a gene encoding the rate-limiting CS-synthesizing enzyme, i.e., CS-N-acetylgalactosaminytransferase-1 (T1).

Methods: T1 knockout (T1KO) mice were generated from the C57BL/6N strain and C57BL/6N were prepared as wild type (WT). Diabetes was induced through streptozotocin injection in 6-week-old male mice. All data were obtained 3 weeks after streptozotocin injection.

Results: In the heat radiant test, while thermal nociception in nondiabetic WT and T1KO mice were normal and significantly disrupted in diabetic WT mice, that in diabetic T1KO mice was preserved. The number of planar peripheral nerve fibers was also significantly decreased in diabetic WT mice; however, that in diabetic T1KO mice was relatively normal. Furthermore, immunohistochemistry revealed loss of calcitonin gene-related peptide-positive neurons in the dorsal root ganglia (DRG) in diabetic WT mice, which contains a cluster of sensory neuron bodies. In contrast, those neurons were protected in diabetic T1KO mice. Hence, nociception and thermoception are preserved in diabetic T1KO mice. To investigate the mechanisms underlying these events, we analyzed gene expression in DRG through real-time polymerase chain reaction and confirmed the suppression of caspase-3 and caspase-9 in diabetic WT mice, compared to those in diabetic WT mice. However, levels of Bcl2, TNF-α, MMP9, and reactive oxygen species-related enzymes (HO-1, NDX) did not differ significantly between WT and T1KO diabetic mice.

Conclusions: Reduced CS production is suggested to have potentially beneficial effects on preventing DN by suppressing apoptotic signaling and could be a cutting-edge target of clinical application.

**Two-Way Orthogonal Partial Least Squares (O2PLS) Analysis of the Lipidome and Transcriptome in Prediabetic and Diabetic Neuropathy**

KAI GUO, EVA L. FELDMAN, JUNGUUK HUR, Grand Forks, ND, Ann Arbor, MI

Peripheral neuropathy (PN) is a common complication of prediabetes and type 2 diabetes (T2D) for which there are limited treatment options. Using mouse models of prediabetes and T2D we have demonstrated that dietary reversal (DR) corrects the PN phenotype. To identify the mechanisms that underlie PN development and reversal, we employed an omics-based approach. This was achieved by integrating transcriptomic and lipidomic datasets derived from mouse sciatic nerve using two-way Orthogonal Partial Least Squares (O2PLS) analysis, a platform that is useful in uncovering the large-scale organization of metabolic networks. Sciatic nerve was isolated from five groups of mice that consisted of controls, high-fat (HF) fed mice (prediabetic), HF mice injected with low dose STZ (T2D), HF mice subjected to 8 week dietary reversal (DR) and T2D-DR. Tissue was processed for gene expression by mRNA-seq or for lipid species profiling by untargeted shotgun lipidomics. A total of 40,257 lipid species and 29 novel species, were identified based on these analyses and primarily consisted of triacylglycerols (TG) and diacylglycerols (DG). Moreover, a comprehensive lipid-gene interaction network was constructed based on these genes and lipid species. This study demonstrates that O2PLS can provide significant and biologically relevant coordination between gene
expression and lipid levels can offer new insights into our understanding of the metabolic networks underlying PN in T2D.

Supported by: National Institutes of Health (R24RO182841 to E.L.F., National Institute of Diabetes and Digestive and Kidney Diseases (DK076189), (25034-75 to J.H.), University of North Dakota (to K.G.), National Institutes of Health (R01DK107956); Novo Nordisk Foundation (NNF14SB002), Noblestein, Nathan and Rose Research Fund; Sinai Medical Staff Foundation; A. Alfred Taubman Medical Research Institute

**COMPLICATIONS—NEUROPATHY**

**549-P**

**Beneficial Effects of Xanthine Oxidase Inhibitor, Topiloxostat, on Experimental Diabetic Neuropathy in Mice**

HIROKI MIYUKAMI, REMINA KOYAMA, KAZUHIISA TAKAHASHI, SHO OSONOI, SAGRI OGASAWARA, SORIYUKI YAGIHASHI, Hirosaki, Japan

Xanthine oxidoreductase (XOR) catalyzes the final step of the purine metabolism from xanthine to urate. XOR is then converted into xanthine oxidase (XO), incurring tissue damage when XO after XOR is activated such as in diabetes. The aim of this study is to evaluate the pathogenic role of XOR/XO in the development of diabetic polyneuropathy (DPN), and to clarify whether suppression of XO is beneficial for DPN. CNS868 (CS7) and DB/db mice (db) 5-week of age were treated daily with a new potent XO-inhibitor, topiloxostat (T), 1mg/kg (dbT1) and 2mg/kg (dbT2) ad libitum with conventional laboratory chow for 8 weeks. During experimental period, glycemic levels, nerve conduction velocity (NCVs) and tail flick response were regularly monitored. At end, following the measurement of sciatic nerve blood flow (SNBF) by laser doppler, mice were killed for the evaluation of the sciatic nerve (SN), intra-epidermal nerve fiber density (IENFD) and lba-1 positive macrophage infiltration (MI) into SN. Glycemic levels were comparable among all diabetic groups. There was no significant delay of NCVs and elevated perception threshold of tail flick in db compared to CS7. To treatopathy improved these measures in a dose-dependent manner (p<0.05 dbT2 vs. CS7 for NCVs, and p<0.05 db vs. dbT1 and p<0.01 db vs. dbT2 for tail flick). XO activity in SN was dose-dependently suppressed compared to db (p<0.05 vs. dbT1, p<0.01 vs. vs. dbT2). To treatopathy at a high dose also corrected reduced SNBF and IENFD in db (p<0.01 dbT2 vs. db for both). There was a significant increase in lba-1 positive macrophages in SN of db compared to CS7 after 4 week-treatment (p<0.01). MI was significantly reduced in dbT1 and dbT2 (p<0.01). In contrast, there was no significant difference in MI at 8 week-treatment among all these groups. Results indicated the possible implication of XOR/XO metabolism in the pathophysiology of DPN and Tod to be a promising compound for the treatment of DPN.

**550-P**

**A Magnetic Resonance Imaging Volumetry Study of Regional Brain Atrophy in Diabetic Peripheral Neuropathy**

DINESH KUMAR, FRANCESCA HEBBERBERG-BONS, JAIN D. WILKINSON, RAJIV GANDHI, SOLOMON TSEFAYE, Sheffield, United Kingdom

Aims: Diabetic neuropathy (DN) is a serious complication which is hitherto considered a disease of the peripheral nervous system. In this study we sought to investigate significant differences in brain morphology in DN. The aim of this study was to identify significant brain volume changes that were specific to DN (painful and painless DN). Methods: 102 patients with diabetes (34 No-DN, 34 Painless DN and 34 Painful DN) and 34 healthy volunteers underwent detailed clinical and neurophysiological assessments. All subjects underwent 3-dimensional T1-weighted brain MRI (3T, Philips). Brain volume analysis was performed using Sienax (www.fmrib.ox.ac.uk/fsl) and Freesurfer (http://surfer.nmr.mgh.harvard.edu/).

Results: Groups were matched for age and gender. Total brain volume was significantly lower painful DN [1407 (10.7) ml] and painless DN [1399.5 (83.8) ml] compared to HV [1457.2 (72.9) ml] and No DN [1437.2 (90.9) ml]: ANOVA p<0.01. Total gray matter volume was significantly lower in painful DN [713.9 (67.7) ml] and painless DN [717.2 (42.4) ml] compared to controls [HV 758.4 (46.5); p<0.01, No DN [747.3 (41.1); p=0.015]. There were no significant differences in white matter (ANOVA p=0.19) and CSF (ANOVA p=0.23) volumes. Painful DN subjects had significantly lower cortical thickness in the right postcentral gyrus [1.83 (0.14) mm vs. HV 1.91 (0.13) mm; p=0.02]; left precentral gyrus [2.31 (0.16) mm vs. HV 2.39 (0.12) mm; p=0.02] and no DN [2.38 (0.14) mm; p=0.04]; and left insula [2.81 (0.15) mm vs. HV 2.97 (0.14) mm; p=0.01].

Conclusion: This is the largest cohort study of brain volume changes in subjects with DN examined to date. We have demonstrated significant reduction in grey matter volume in painful and painless DN subjects. In painful DN this is localised within the somatomotor cortex and insula. These findings highlight significant CNS involvement in DN that provides clues to the pathogenesis of this condition.

Supported by: JDRF

**551-P**

**Large-Scale DNA Methylation Profiling of Human Diabetic Peripheral Neuropathy in Subjects with Type 2 Diabetes Mellitus**

KAI GUO, SARAH ELZINGA, STEPHANIE EID, CLAUDIA FIGUEROA-ROMERO, BRET A. MCGREGOR, GUILLERMO DE ANDA-JÁUREGUI, CRYSTAL PACUT, EVA L. FELDMAN, JUNGUK HUR, Grant Forks, MD, Ann Arbor, MI

Diabetic peripheral neuropathy (DPN) is the most common complication of diabetes. Emerging evidence that aberrant DNA methylation may play a critical role in the pathogenesis of diabetic complications. Yet, its involvement in DPN is not fully characterized. In this study, we performed a large-scale genome-wide methylation profiling of sural nerve samples obtained from subjects with type 2 diabetes mellitus (T2DM) using Reduced Representation Bisulfite Sequencing (RRBS). A total of 78 samples were sequenced and mapped to the human reference genome. Differential analysis was performed on two groups, identified by our previous transcriptomic analysis of the same samples, which showed significantly different HbA1c levels: Group 1 (>8.5%) and Group 2 (>7.0%). Using MethyKit R package, with an adjusted p-value < 0.01 and 15% methylation change as significance cutoffs, we identified 2,066 differentially methylated CpG sites and 440 regions, corresponding to 1,519 and 429 unique differentially methylated genes (DMGs). These genes were highly enriched in biological processes related to nervous system development, neuron fate specification and neurodifferentiation. KEGG pathway enrichment analysis demonstrated that genes involved in cancer, ECM-receptor interaction and axon guidance pathways were significantly differentially methylated between the two groups, highlighting the importance of DNA methylation in DPN pathogenesis.

In summary, we demonstrate that type 2 diabetic patients with peripheral neuropathy and high HbA1c show distinct variations in sural nerve methylation, suggesting that DNA methylation and DPN are associated and that these associations are at least in part HbA1c-dependent. Our results provide new insights into the role of HbA1c in epigenetic variation, and identify candidate genes relevant to the pathogenesis of DPN in human sural nerves of subjects with T2DM.

Supported by: National Institutes of Health (R24RO182841 to E.L.F., National Institute of Diabetes and Digestive and Kidney Diseases (DK076189), (25034-75 to J.H.), University of North Dakota (to K.G.)

**552-P**

**Prevalence of Peripheral Neuropathy in Prediabetes**

UAZMAN ALAM, DIABETES AND ENDOCRINE RESEARCH GROUP, UNIVERSITY OF LIVERPOOL, EARLY NEUROPATHY ASSESSMENT GROUP, MANCHESTER, Liverpool, United Kingdom

Objectives: There are conflicting evidence regarding the relationship of peripheral neuropathy in prediabetes. Our aim was to determine the prevalence of peripheral neuropathy in prediabetes through a systematic literature review and meta-analysis.

Methods: Five electronic databases, namely MEDLINE, EMBASE, PubMed, Web of Science and Cochrane Central Register of Controlled Trials were searched for studies published up to October 2017. Original full studies were included that provided prevalence data for a population with prediabetes, who were over 18 years of age. Additional studies were identified from reference lists and two reviewers independently identified eligible studies on predefined inclusion criteria.

Results: In total, 1,314 studies were identified after duplicates were removed and subsequently 1,255 were excluded. Of the 59 remaining studies, 23 studies (n=6,494) met the inclusion criteria for the meta-analysis. The pooled prevalence estimate of neuropathy in prediabetes was 18% (95% CI: 13-22%) with a marked level of heterogeneity (I2 = 97%). The high level of heterogeneity between studies was partly explained by the method of neuropathy assessment. Subgroup analyses based on the method of neuropathy assessment was evaluated and the prevalence was highly dependent on the method of assessment. The prevalence depending on the type of test used was: quantitative tests: 16% (95% CI: 3-30%, I2 = 95%), physical examination: 24% (95% CI: 7-40%, I2 = 83%), questionnaires: 8% (95% CI: 2-13%, I2 = 57%) and combination(s) of the three: 18% (95% CI: 13-24%, I2 = 97%).

Conclusions: There is a higher than expected prevalence of peripheral neuropathy in prediabetes. Future large, population based studies using accurate and quantitative means of identifying neuropathy are required and an internationally agreed definition as to what constitutes prediabetic neuropathy is required.
553-P

LXRs Protect DRG Neurons from High-Fat Diet-Induced ER Stress and Alloeldia

VIRGINIE ALIDIBERT, Chicago, Il

Painful diabetic neuropathy (DN) affecting small sensory neurons is one of the most common complications of obesity and type 2 diabetes. While emerging clinical evidence demonstrates that DN is associated with type 2 diabetes, the complex molecular and cellular neurobiology triggering the disease is unknown. Emerging evidence demonstrates the important contribution of complex pathways including endoplasmic reticulum stress and inflammation. Recent DMCIs data analyzing peripheral nervous tissue (Dorsal root ganglia (DRG) and associated nerves) of obese individuals have also highlighted alterations in lipid nuclear receptors, which provide novel insight into the onset of DN. Liver X Receptors (LXR) α and β are nuclear transcription factors that respond to cholesterol or fatty acid metabolites. Nuclear LXRs control gene programs in liver cells, adipocytes, and macrophages to regulate lipid metabolism, inflammation and ER stress though the specific physiological role of LXRs in neurons is difficult to interpret given its broad tissue expression. Our tissue specific deletion model unmasks an important role of LXR in small sensory neurons in type 2 DN pathogenesis. Our results show that LXR deletion in sensory neurons worsens the hyper-sensitivity induced by a High fat Diet (HFD) associated with changes in DRG gene. In addition, treatment with the LXR agonist GW4966 improves the HFD-induced mechanical allodynia in vivo and protects mice DRG sensory neurons from lipid-induced ER stress in vitro and in vivo (tibia-muscle), further confirming a protective role for LXR in DN. Our data suggest that the lipid sensor LXRs in small sensory neurons could respond to dietary lipid to potentially maintain normal PNS function in the face of high-fat nutrition.

554-P

Mechanisms of Therapeutic Effects of Conditioned Media from Cultured Dental Pulp Stem Cells on Diabetic Polyneuropathy

ERIKO MAKINO, NUBUHIISA NAKAMURA, MEGUMI MIYABE, MIYUZO ITO, SAKI KANADA, MASASI HATA, TOMOKAZU SAIO, HIDEKI KAMIYA, JIRO NAKA-MURA, KEN MIYAZAWA, SHIGEMI GOTO, TATSUKI MATSUBARA, KEIKO NARUSE, Nagoya, Japan; NAGAKIJE, Japan

Stem cell transplantation is expected to become a novel therapy for diabetic polyneuropathy. Dental pulp stem cells (DPSC) are an attractive cell source for cell transplantation due to their low immunogenicity, high proliferative capacity, and multipotency. This study aimed to determine the possible therapeutic effects of conditioned media from DPSCs (DPSC-CM) on diabetic polyneuropathy. DPSCs were isolated and cultured from the mandibular incisors of 6-week-old male Sprague-Dawley (SD) rats. Diabetes was induced at 6-weeks by administering STZ. DPSC-CM was administrated to the unilateral hindlimb skeletal muscles of both the diabetic and normal rats 8 weeks after the administration of STZ, and the measurements were performed 4 weeks after DPSC-CM administration. Administration of DPSC-CM significantly improved the delay of the sciatic nerve motor/sensory conduction velocity and reduced sciatic nerve blood flow in diabetic rats. TNF-α and CD68 gene expression in the sciatic nerves tended to increase in the diabetic group, which showed a decreasing trend by administration of DPSC-CM. Capillary density in the hindlimb skeletal muscle was decreased in diabetic rats. DPSC-CM significantly increased capillary/muscle ratio in the hindlimb skeletal muscles in the diabetic rats. It was revealed that intramuscular administration of DPSC-CM was effective for diabetic polyneuropathy at least in part by improving nerve/muscle blood flow and suppressing inflammation. These results indicate that DPSC-CM could be a novel therapy for diabetic polyneuropathy.

555-P

The Impact of Normoglycemia in Reducing Microvascular Complications in Patients with Type 2 Diabetes—A Follow-Up Study

MITRA TAVAKOLI, FUKASHI ISHIBASHI, Exeter, United Kingdom; HATSUAKI, Japan

Aim: Hyperglycemia is associated with increased risk of microvascular complications in patients with type 2 diabetes (T2DM). The aim of the present study is to investigate whether reduction of the levels of HbA1c by tight glycemic control (GC) decreases the rate of microvascular complications and improves the neurological measures in T2DM.

Methods: Detailed clinical, neurological examinations including cutaneous confoal microscopy (CCM), were performed in 141 patients with poorly controlled type 2 diabetes (mean age 53, Duration diabetes: 9 years) at the baseline and 60 age-matched control subjects and followed-up with GC for 4 years. Nephropathy and Retinopathy also assessed. Patients were stratified according to mean HbA1c level during follow-up.

Results: At baseline CCM showed significant nerve fiber damage in all patients compared to controls. Despite strict GC and improvement in mean HbA1c by around 2.8%, overall the cumulative incidence of neuropathy increased from 12.7% at baseline to 21.3% and retinopathy increased from 21.3% to 39.5%. However the cumulative incidence of nephropathy reduced from 37.6% to 22%. Tight GC was effective in improving neuropathy only in those with very poor Control at the Baseline. The interval changes in HbA1c levels were correlated with the interval changes in CCM measures and neurophysiological tests. The results showed one percent reduction in HbA1c levels per year significantly improved CCM measures and neurophysiological dysfunctions. Based on the results of this study, for improving neuropathy, only HbA1c close to 6.5% is effective for improvement in structure and function of the corneal nerves.

Conclusion: This study showed that the GC was just improved neuropathy among microvascular complications. Glucose control did only improve neurophysiological and corneal nerve measurements when near-normoglycemia was reached. Despite tight GC, the retinopathy progressed in patients with type 2 diabetes at this cohort.

556-P

Vitamin D Supplementation and Microcirculation Parameters in Diabetic Patients with Polyneuropathy

ANNA P. STEPANOVA, TATYANA L. KARONOVA, EDWARD B. JUDE, Saint Petersburg, Russian Federation; Manchester, United Kingdom

Type 2 diabetes mellitus (T2DM) is often combined with vitamin D (VD) deficiency. It is known that VD affects glycemic control as well as systemic inflammation and could play a role in diabetic neuropathy (DN) pathogenesis. High VD dose supplementation decreases impaired microcirculation in diabetic patients and reduces DN severity. NTSS-9, NDS scales were used, 25(OH)D, HbA1c were studied in 24(12) patients with T2DM and DN. Parameters of microcirculation (value of perfusion - M, standard deviation - σ, Kv - coefficient of microcirculation) by laser Doppler fluorometry (LARK-M, Russia) and after 24 weeks of VD supplementation. Inclusion criteria: T2DM duration more than 5 years, HbA1c ≥50%, NDS index 4 and more, signed IC. Patients were randomized in to two groups: 5000 IU (group I) and 10000 IU (group II) per week cholecalciferol treatment without hypoglycemic treatment changes. At baseline the two groups were comparable by sex, age, BMI, HbA1c level. We included in group I twelve pts (6F) aged 56.1±5.4 years and in group II we included 12 pts (6F), mean age 51.3±5.9, HbA1c: 6.4±0.6%, 25(OH)D 20.9±4.1 nmol/l. Baseline NDS index did not differ between the two groups 10.1±3.3 and 12.3±4.7 accordingly, as well as the NTSS-9 index 15.8±5.2 and 17.1±6.8 (p=0.05). Parameters of microcirculation were the same M=10.6±3.1 and 12.3±2.7, 75%PI, α=5.3±0.79 and 4.4±0.15, Κv=11.3±3.59 and 10.6±2.93. After 24 weeks of VD treatment we did not find changes in group I - HbA1c 8.1±0.4%, 25(OH)D 24.7±2.5 (p=0.07), M=10.3±0.14 (p=0.08), α=4.8±0.56 (p=0.05) and Κv=11.8±2.38 (p=0.87). HbA1c significantly decreased till 7.4±0.7% (p=0.02) in group II. 25(OH)D level increased to 60.9±3.1 (p=0.003). We found improvement of all microcirculation parameters M=19.5±2.52 (p=0.003), α=6.05±0.93 (p=0.005), Κv=13.3±3.15 (p=0.017) compared to baseline. High dose of VD supplementation could improve microcirculation parameters in T2DM patients with DN.

Supported By: National Institutes of Health

557-P

The Effect and Molecular Mechanism of Pancreatic Kallikrein in Painful Diabetic Neuropathy Based on CX3C1L1/CX3CR1 Pathway

XU XIANG, JIN HUI, XU LAN, WEN, China

Objective: This study evaluated the effect and molecular mechanism of pancreatic kallikrein (PKK) in improving mechanical allodynia in STZ-induced C57 mice, an animal model of type 1 diabetes, based on CX3C1L1/CX3CR1 pathway.

Methods: Male C57 mice, weighing 20-23g, were fasted overnight for 12h (20:00-8:00 next day) and injected with STZ (100mg/kg) to induce type 1 diabetes model. 24 diabetic mice were divided into PKK-1 group (PKK 6u/kg/d, ip, n=8), PKK-2 group (PKK 60u/kg/d, ip, n=8) and DNS group (0.9% NaCl 0.15ml/d, ip, n=8). Eight normal C57 mice were injected with PKK (6u/kg/d, ip) as the NFK group. The mechanical allodynia of each group was evaluated...
from 1h to 5 weeks after PKK injection. The expression of CX3CL1/CX3CR1 at the lumbar spinal cord was also measured at the 5th week using Western blot analysis.

Results: 1) More than 80% of C57 mice were tested FBG>11.1mmol/L at the 7th day after STZ injection and divided into the diabetic group. 2) Compared with the normal mice, we showed that the diabetic mice developed mechanical allodynia at the early stage of diabetes. Meanwhile, The intraperitoneal injection of PKK could decrease such mechanical allodynia in a dose-independent manner. 3) Compared with the DNS group, the intraperitoneal injection of PKK significantly attenuated the expression of CX3CL1/ CX3CR1 at the dorsal horn. This study may contribute to a better understanding of the therapeutic effect and mechanism of PKK on painful diabetic neuropathy.

Supported By: Health and Family Planning Commission of Wuxi, China (N2ZH1406)

**Effect of Diabetes on Peripheral Neuropathy in an Adult U.S. Population**

MUHDEEN T. OLAIYI, ROBERT L. HANSON, KAREN G. KAVENA, MADHUMITA SINHA, ROBERT NELSON, WILLIAM C. KNOWLER, Phoenix, AZ

Background: Peripheral neuropathy (PN) is a diabetes complication but also occurs without diabetes. The effect of diabetes on PN is not well quantified.

Methods: Subjects ≥ 18 years old had a health exam, including an OGTT for diabetes. Distal sensory PN, assessed using 3 graded Semmes Weinstein monofilaments, was classified as none (all filaments), latent (insensitive to 1 g filament), clinical (mild [insensitivity to 10 g] or severe [75 g]). Associations with PN were assessed using ordinal logistic regression assuming equal coefficients across classes of PN.

Results: In 1564 subjects (median age 42 years, 50% women, 58% Americans), PN was latent or worse in 68.9% (95% CI 66.7-71.2), clinical in 11.2% (CI 9.7-12.9), and associated with male sex, older age, and worse glucose regulation (Figure). Age-sex-race-adjusted prevalence was greater at the lumbar spinal cord was also measured at the 5th week using Western blot analysis.

**Prevalence of Cardiovascular Autonomic Neuropathy and Gastroparesis Symptoms among Adults with Type 2 Diabetes Who Attend a Primary Health Care Center**

LINA ALUALLI, TURKI ALHARBI, AYLA TOURKMANI, Riyadh, Saudi Arabia

Introduction: Cardiovascular autonomic neuropathy (CAN) and gastroparesis are two forms of diabetic autonomic neuropathy that could affect the quality of life of the patients and carry significant morbidity and mortality outcomes. This study aimed to estimate the prevalence and risk factors of both CAN and gastroparesis symptoms (GPS) among patients with type 2 diabetes (T2D).

Methods: A cross-sectional study was conducted among 347 adults (≥ 18 years) with T2D from April 1 - December 15, 2017. CAN was defined by the presence of any of the following: resting tachycardia (RT), resting heart rate > 100 bpm, orthostatic hypotension OH (a fall in systolic blood pressure (SBP) by > 20 mmHg or a fall in diastolic blood pressure by > 10 mmHg within 3 minutes of standing) or prolonged corrected QT interval (QTc) in the electrocardiogram (> 0.47 seconds in females, and > 0.45 seconds in males). The GPS were assessed using a validated questionnaire: Gastroparesis Cardinal Symptom Index (GCSI). GCSI score ≥ 1.9 signified definite GPS.

Results: The mean age was 55.6 ± 10.0 years. The mean HbA1c and T2D duration was 8 ± 1.6 and 10.6 ± 6.9 years, respectively. CAN was present in 15.6%; 2.9% with OH, 5.8% with RT and 8.4% with prolonged QTc. Anti-hypertensive agents (anti-HTN), body mass index (BMI), SBP, triglycerides and HbA1c were significantly higher in patients with CAN, P=0.05. Prolonged T2D duration (OR= 1.07, 95% CI 1.1-1.14; p=0.04) and anti-HTN (OR= 5.2, 95% CI 1.2-23; p=0.03) were independently associated with CAN. GPS were present in 3.2% and were significantly associated with higher BMI, P=0.05. Metformin use emerged as the single significant independent predictor of the presence of at least one GPS (OR=5.2, 95% CI 1.8-14.7, p=0.002).

Conclusion: The prevalence of CAN among T2D subjects was 15.5%. Prolonged T2D duration and anti-HTN emerged as significant predictors of CAN. The prevalence of GPS was 3.2% and was independently associated with metformin use.

**Sex Differences in Neuropathy and Neuropathic Pain in Long-Standing Diabetes—Results from the Canadian Study of Longevity in Type 1 Diabetes**

NANCY CARDINEZ, LEF ERIK LOVBLOM, JOHNNY-WEI BAI, ALON ABRAHAM, EVAN J. LEWIS, DANIEL SCARR, JULIE A. LOVSHIN, YULIYA TVYN, GENEVIEVE BOULET, MOHAMMED FAROOQI, ANDREJ ORSZAG, ALANNA WEISMAN, HARRY A. KEENAN, MICHAEL H. BRENT, NARINDER PAUL, VERA BRIL, DAVID CHERNEY, BRUCE A. PERKINS, Toronto, ON, Canada; Hamilton, ON, Canada; Boston, MA, London, ON, Canada

Neuropathy and neuropathic pain are common complications in T1D. We aimed to determine if sex-specific differences in the prevalence of neuropathic pain and neuropathy exist in patients with longstanding T1D. In Phase 1 of the study, 361 Canadians with ≥50 years of T1D completed questionnaires which included subjective assessment for neuropathy defined by Michigan Neuropathy Screening Instrument Questionnaire score ≥3, termed NEUROPATHYqsi. In the Phase 1 cohort, more females than males reported neuropathic pain (OR=3.42; p=0.033), but the presence of neuropathy (NEUROPATHYqsi) did not differ by sex (OR=2.72) females vs. 66(43%) males, p=0.02), and thus neuropathic pain was independent of the presence of neuropathy (adjusted OR for neuropathic pain in females compared to males, 2.7 [1.4-5.3; p=0.002]). In the Phase 2 participants, neuropathic pain was similar between the sexes (29% females vs. 21% males, p=0.43) while NEUROPATHYqsi was less prevalent among females (83% females vs. 97% males, p=0.05). Though not statistically significant, in a combined analysis of Phase 2 participants adjusted for NEUROPATHYqsi, females had a tendency to a higher adjusted OR for neuropathic pain compared to males [OR 2.0 (95% CI 0.8-4.7), p=0.11].

In conclusion, in patients with longstanding T1D, neuropathic pain appears to be greater among females compared to males independent of the presence of neuropathy. Further research to confirm that objective neuropathy measures are required to further confirm and address these sex-specific differences.

Supported By: JDRF (17-2013-312)
Sensory Cutoff Value for Predicting Postural Instability in People with Peripheral Neuropathy Secondary to Diabetes

NAY LINN AUNING, STACEY A. MEARDON, CHIA-CHENG LIN, ROBERT J. TANENBERG, Greenville, NC

People with peripheral neuropathy (PN) secondary to diabetes have higher risks of falls due to loss of the somatosensation of the feet. The purpose of this study was to investigate the cutoff values of the vibration threshold and the monofilament test to predict postural instability. Ten healthy younger adults, ten healthy older adults and ten people with PN secondary to diabetes were recruited in this study. A handheld biothesiometer and a set of monofilaments were used to measure the vibration threshold (VT) and tactile sensitivity (TS), respectively. VT and TS were measured at six different sites on the plantar surface, including big toe, 1st metatarsus, little toe, 5th metatarsus, middle arch, and calcaneus (heel), plus the lateral and medial malleoli. Subjects also underwent a Sensory Organization Test (SOT) to identify postural instability, defined as equilibrium scores less than 10 age matched norms. Linear regression was used to determine which site(s) was able to predict the balance test performance. Receiver operating characteristic curves were used to compute the VT and TS cutoff values associated with postural instability. A cutoff value of 10V for lateral malleous VT was able to predict postural abnormality with 100% Sensitivity and 54.5% Specificity. A cutoff value of 3.61 for middle arch TS was able to predict postural abnormality with 100% Sensitivity and 86.4% Specificity. Postural instability appears earlier than the current recommended clinical cutoff values for peripheral neuropathy (25V for VT and 5.07 for TS). Although current cutoff values of the vibration threshold and the monofilament test are useful for detecting a propensity for neuropathic foot ulcer, they may not be adequate for detecting early postural instability. Fall prevention strategies may be needed early in the progression of PN.

The Prevalence and Characteristics of Diabetic Polyneuropathy in Japanese Type 2 Diabetic Patient

HIDEKI KAMIYA, ATSUKO WATARAI, MASAYUKI BABA, RIMEI NISHIMURA, NAOKO TAJIMA, JIRO NAKAMURA, Nagakute, Japan, Nagoya, Japan, Aomori, Japan, Tokyo, Japan

This study aims to investigate the prevalence and characteristics of diabetic polyneuropathy (DPN) in type 2 diabetic patients registered in the Japan Diabetes Complication and its Prevention Prospective (JDCP) study. In the JDCP study, 6,338 diabetic patients who had been treated by diabetes specialists were registered in 2007-8. Of these, 5,451 patients with type 2 diabetes (61.4 years-old, duration of diabetes 10. 8 years, BMI 24.5 and HbA1c 7.4% who could be evaluated for DPN were analyzed by using t-test, chi-square test and logistic regression analysis. The diagnosis of DPN was performed by using simple diagnostic criterion for diabetic polyneuropathy proposed by Diabetic Neuropathy Study Group in Japan. This criterion should meet two or more of the following three items: 1) sensory symptoms (SS) considered to be due to DPN, 2) bilaterally decreased or absent Achilles tendon reflex (ATR) and 3) decreased vibration perception threshold (VPT) in bilateral malleolar. The prevalence of positive SS, bilaterally decreased/absent ATR and symmetric decrease in VPT were 25.8%, 40.9% and 48.1%, respectively. Based on simple diagnostic criterion, DPN was observed in 35.8% of the total. The decrease/absence of bilateral ATR showed high sensitivity (87.2%) and specificity (84.8%) in the diagnosis of DPN.

In the group with DPN, we investigated the odds ratio (OR) of covariates for neuropathy and found that the age (OR 1.58, p<0.001), the duration of diabetes (OR 1.32, p<0.001), BMI (OR 1.20, p<0.001), T-cho (OR 1.06, p<0.01), insulin therapy (OR 1.62, p<0.001), systolic blood pressure (OR 1.06, p<0.01), HbA1c (OR 1.17, p<0.001), oral administration of biguanide (OR 1.19, p<0.01) and exercise therapy (OR 0.83, p<0.05) showed significant. Baseline survey of the JDCP study, the prevalence of DPN in type 2 diabetic patients was similar to that reported previously, suggesting the possibility that the evaluation of bilateral ATR is useful for the diagnosis of DPN.

Usefulness of a Point-of-Care Sural Nerve Conduction Device (DPNCheck™) for Evaluation of Diabetic Symmetric Sensorimotor Polyneuropathy in Japan

YUKA SHIBATA, HIDEKI KAMIYA, TATSUHIITO HIMENO, MIKO MOTEI, HIROMI SHIMODA, MAKOTO KATO, YUCHIHO YAMADA, EMRI MIURA-YURA, MASAKI KUNI, SHIN TSUNEKAWA, YOSHIO KATO, JIRO NAKAMURA, Nagakute, Japan

Nerve conduction study (NCS) is a reliable examination to diagnose and to evaluate diabetic symmetric sensorimotor polyneuropathy (DSPN). However, NCS is not feasible in daily medical practice, because it requires skilled laboratory technicians and an expensive equipment. A point-of-care device, DPNCheck™ can measure sural nerve (SN) action potential amplitude (Amp) and conduction velocity (CV) in less than 5 minutes without special techniques. Here, we evaluated the accuracy and the usefulness of DPNCheck™ for diagnosis of DSPN in Japanese diabetic patients. We selected 207 diabetic patients. 1. We examined bilateral SN both by electromyography (EM) and DPNCheck™ and compared the differences. 2. To evaluate the reproducibility and inter-rater reliability of DPNCheck™, Amp and CV of SN were measured twice by an examiner and once by another examiner. 3. Based on the results of EM, we classified the severity of DSPN into 3 grades as follows; grade 0: Amp of SN (SNAP) 5µV or more and Amp of tibial nerve (CMAP) 5V or more, grade 1: SNAP<5µV and CMAP<5mV or more, and grade 2: SNAP<5µV and CMAP<5mV. Then, a formula to predict the grades of DSPN severity by using the Amp and CV from DPNCheck™ was created. For statistical analyses SPSS was used. 1. The correlation coefficient (R) for CV and Amp between DPNCheck™ and EM were R=0.7683 and 0.6178, respectively. 2. The reproducibility and inter-rater reliability of DPNCheck™ was “superior” and “acceptable”, respectively. 3. To predict the severity of DSPN by DPNCheck™ was as follows; “grade 0”=2.235±0.008×Age-0.015×CV-0.041×Amp”. The grade calculated by this formula was relatively “acceptable” compared with the real grade determined by EM (correlation coefficient: R=0.645). These results indicate that DPNCheck™ is a useful device to measure SN functions in Japanese diabetic patients and should be used more frequently in the bedside to diagnose and evaluate DSPN.

Palmitoylethanolamide in Add-on to Alpha Lipoic Acid for Control of Symptoms of Diabetic Peripheral Neuropathy

ERNESTO MADDALONI, ANNA RITA MAURIZI, ALESSANDRA MINUTOLO, ELVIRA FIORITI, ROSSELLA DEL TORO, ANDA MIHAELA NACIU, SILVIA PIERALICE, MILENA M. ROSATI, SILVIA MANFIRINI, PAOLO POZZOLI, Rome, Italy

Background: Palmitoylethanolamide (PEA) is an amide with “autocoid local inflammation antagonism” effects, protecting nerve degeneration due to mast cell degranulation. PEA add-on to alpha-lipoic acid (ALA) is successfully used as treatment of neuropathic pain, but there are no data in diabetic peripheral neuropathy (DPN) specifically.

Aim: To evaluate whether PEA in add-on to ALA has potentials in controlling DPN symptoms.

Methods: In this pilot longitudinal observational study, clinical and biochemical data from ninety-eight consecutive subjects with type 1 diabetes (T1D) evaluated for DPN symptoms between January and July 2017 in our outpatient clinic were retrospectively retrieved. DPN symptoms were assessed by Neuropathy Symptoms Score (NSS). Follow-up data were retrieved for patients with NSS ≥2 and receiving treatment with ALA 600mg/day a PEA 600mg/day or receiving no treatment.

Results: NSS was ≥3 in 34 (34.7%) subjects. Of these, 17 were treated with ALA a PEA (9 with ALA in monotherapy and 8 with PEA in add-on to ALA), and 17 were not treated. After a mean follow-up of 6.1±3.4 months, NSS was ≥3 in 76.5% of non-treated subjects vs. 29.4% of treated subjects (p=0.01). The percentage of subjects with NSS≥3 did not differ between subjects treated with ALA vs. those treated with ALA+PEA (p=0.62). The mean time for symptoms resolution (NSS=3) was lower in subject treated with ALA+PEA than in those treated with ALA in monotherapy (14.0±6.8 vs. 25.0±9.1 days, p=0.05). Among treated subjects, baseline HDL-cholesterol was inversely related to the time to symptoms resolution (p=0.026).

Conclusions: PEA add-on to ALA accelerates the resolution of neuropathic symptoms in T1D subjects with DPN. This study also suggests HDL-cholesterol may be a biomarker for the response to treatment with ALA + PEA.

Supported By: LJ Pharma SR.L.
**Complications—Neuropathy**

**565-P**

A Novel Severity Classification of Diabetic Polyneuropathy Based on Nerve Conduction Study and ECG

HIROMI SHIMODA, HIDEKI KAMIYA, ATSUKO WATARAI, TATSUHIITO HIMENO, YUKA SHIBATA, MIKIO MOTEIGI, MAKOTO KATO, YUICHIRO YAMADA, EMRI MIURA-YURA, MASAKI KONDO, SHIN TSUNEKAWA, YOSHIRO KATO, JIRO NAKAMURA, Nagakute, Japan, Nagoya, Japan

In this study, we propose a novel DPN severity classification based on coefficient of variance of R-R interval on ECG (CVVR) and nerve conduction study (NCS). The subjects consisted of 182 patients (mean age 58.9 ± years; duration of diabetes 10.2 years, HbA1c 9.72% and BMI 26.0) with type 2 diabetes admitted to our hospital from 2015 to 2017. Based on NCS and CVVR during rest, the subjects were classified into six categories as follows; 1) N0C0: normal nerve sensory action potential (SP) <5µV and nilb nerve compound motor action potential (CP) <5mV + CVVR<2%, 2) N1C0: SP<5 and CP<5 + CVVR<2, 3) N2C0: SP<5 and CP<5 + CVVR<2, 4) N1C1: SP<5 and CP<5 + CVVR<2 + 6) N2C1: SP<5 and CP<5 + CVVR<2. We examined the relationship between each category with urinary albumin excretion rate (logarithmic transformation: LogACR), eGFR, presence/absence of nephropathy (ACR<150mg/gCr and/or eGFR<60ml/min/1.73m2) or retinopathy, and PWV as an index of arteriosclerosis. For statistical analysis, one-way analysis of variance (ANOVA), multiple comparison (Tukey), covariance analysis and logistic regression analysis were used.

The one-way analysis revealed significant differences between each category in terms of age, the duration of diabetes, LogACR, eGFR and PWV. LogACR and PWV were significantly higher in the N2C1 than in the N0C0 (p<0.05). Even after correction with age, duration and gender, a significant difference (p=0.008) between groups was observed in LogACR and a trend (p<0.05) in PWV (p=0.008). In the logistic regression analysis corrected by age, duration and gender, the odds ratio (OR) for retinopathy was 5.36 in N1C0, 11.10 in N1C0, 8.23 in N1C1 and 11.78 in N2C1 compared with N0C0 (p<0.01). The OR for nephropathy in N0C1 was 6.56, 7.91 in N1C1, 15.54 in N2C0 and 23.55 in N2C1 (p<0.05).

Severity classification of DPN based on NCS and CVVR during rest was well correlated to other diabetic complications, suggesting the usefulness of this novel classification to evaluate the severity of DPN.

**566-P**

Secreted Factors from Dental Pulp Stem Cells Ameliorated Diabetic Polyneuropathy in Streptozotocin-Induced Diabetic Mice

EMR IMIURA-YURA, SHIN TSUNEKAWA, TATSUHIITO HIMENO, KEIKO NARUSE, MIKIO MOTEIGI, HIROMI SHIMODA, MAKOTO KATO, YUICHIRO YAMADA, MASAKI KONDO, YOSHIRO KATO, HIDEKI KAMIYA, JIRO NAKAMURA, Nagakute, Japan, Nagoya, Japan

We previously reported that stem cell transplantation into limb skeletal muscle improved diabetic polyneuropathy (DPN) in diabetic animal models without the differentiation of transplanted cells into neurons, suggesting that the improvement was due to a paracrine effect. The aim of our study is to examine which specific the secreted factors from dental pulp stem cells from human exfoliated deciduous teeth (SHED) has a beneficial effect on DPN. Conditioned medium from SHED (SHED-CM) was collected 48 hours after culturing in serum-free DMEM. Incubation of dorsal root ganglion (DRG) neurons excised from C57BL6/J (WT) mice with SHED-CM significantly promoted neurite outgrowth compared that with DMEM. (SHED-CM: 3793.2±907.9 um/neuron, DMEM: 370.9±321.7 um/neuron) Among 4 fractions of SHED-CM according to molecular weight (less than 6kDa, 6-20kDa, 20-100kDa, and greater than 100kDa), only fraction of less than 6kDa significantly increased neurite outgrowth. Incubation of DRG neurons with exosome isolated from CM according to molecular weight (less than 6kDa, 6-20kDa, 20-100kDa, and greater than 100kDa) didn't have any effect on neurite outgrowth, indicating that only neurite outgrowth compared that with DMEM. (SHED-CM: 3793.2±907.9 um/neuron, DMEM: 370.9±321.7 um/neuron) SHED-CM significantly promoted neurite outgrowth, indicating that only soluble factors from SHED-CM contributed to neurite outgrowth of DRG neurons. In in vivo study, 12 weeks after streptozotocin (STZ) administration, 100µl of SHED-CM or DMEM was injected into unilateral lower limb muscle of STZ-induced diabetic mice twice a week over a 4 weeks period. SHED-CM or DMEM injections didn’t change serum glucose levels and body weight in diabetic mice. SHED-CM significantly prevented decline in sensory nerve conduction velocity (SNCV), compared with DMEM. In diabetic mice, capillary number-to-muscle fiber ratio (CNMFR) and intraperidural nerve fiber densities (INFDs) decreased less than those in nondiabetic mice. SHED-CM significantly upregulated the expression of CNMFR, but not INFDs, suggesting that SHED-CM in vivo alleviated SNCV by improving of nerve blood flow. These data suggested that SHED-CM might have potential as a novel strategy for treatment of DPN.

**567-P**

Biological Actions of Glucagon Gene-Derived Peptides in the Peripheral Nervous System of Mice

MIKIO MOTEIGI, TATSUHIITO HIMENO, HIDEKI KAMIYA, HIROMI SHIMODA, MAKOTO KATO, YUICHIRO YAMADA, EMRI MIURA-YURA, MASAKI KONDO, SHIN TSUNEKAWA, YOSHIRO KATO, YOSHITAKA HAYASHI, JIRO NAKAMURA, Nagakute, Japan, Nagoya, Japan

Background: Glucagon gene-derived peptides are produced as glucagon-like peptide 1 (GLP-1) in intestinal L cells and glucagon in pancreatic α cells, and play an important physiological role. However, the physiological roles of these peptides in various tissues are not fully elucidated. In this study, we examined the physiological roles of these peptides in the peripheral nervous system (PNS).

Methods: Expression of glucagon receptor in the PNS was examined in 18-21 week-old C57BL6/J (WT) mice utilizing immunohistochemical staining. Neurite outgrowth was assessed after 24-48 hours of primary culture of dorsal root ganglion (DRG) neurons supplemented with or without glucagon (10^7 to 10^5 mol/l). Furthermore, the sensory function of the plantar pedis was evaluated by thermal plantar test in glucagon gene deficient mice (gcc/-, gcc+/−) of 8, 12, 18, 24, and 30 week-old.

Results: The immunohistological staining validated the expression of glucagon receptor in most DRG neurons and satellite glial cells. In the primary culture of DRG neurons, the neurite length was significantly increased in the group cultured with glucagon. (control: 761.4±294.9 µm/cell, glucagon 10^7 mol/l: 2276.5±985.6 µm/cell, p<0.01). The thermal plantar test revealed a hypersensitivity in 12 week-old gcc−/− mice (WT: 8.8 second, gcc−/−: 6.9, gcc−/−: 5.5, p<0.01: WT vs. gcc−/− in 18 week-old gcc−/− and gcc+/− mice (WT: 8.8, gcc−/−: 7.1, gcc−/−: 6.6, p<0.01: WT vs. gcc−/− or gcc+/−). However, the hypersensitivity disappeared in 24 week-old mice (WT: 8.4, gcc−/−: 8.9, gcc−/−: 8.5).

Discussion: These data suggested that glucagon may have a protective role for DRG neurons. Further investigation should be performed to elucidate the role of glucagon gene-derived peptides in the PNS in the future.

**568-P**

Impaired Hemodynamic Response to Thermal Pain in Painful Diabetic Neuropathy

MARNI GREIG, IAIN D. WILKINSON, DINESH SELVARAJAH, PALLAI RAPPAI SHUHD, RAJIV GANDHI, SOLOMION TESFAYE, Sheffield, United Kingdom

Objective: Painful diabetic peripheral neuropathy (painful-DPN) causes distressing neuropathic pain that is only partially responsive to treatment. A better understanding of CNS correlates of painful-DPN is vital to develop more effective therapeutics. The aim of this study was to measure cerebral perfusion of the pain processing areas of the brain using MR-Dynamic Susceptibility Contrast (MR-DSC) imaging at rest and under experimental pain condition.

Methods: 55 T1DM subjects (20 painful-DPN, 23 painless-DPN, 13 no-DPN) and 19 Healthy Volunteers (HV) underwent detailed clinical and neurophysiological assessment (NISL+7 tests of nerve function; DNA qunomarone) MR images were obtained at 3T using a MR-DSC, T2*-weighted sensitivity Contrast (MR-DSC) imaging at rest and under experimental pain condition.

Results: At baseline, although the mean TTP in the ROIs was shorter in the painful-DPN group (e.g., Rt: M (SD): 9.22 (1.13) vs. HV 9.83 (0.99), no-DPN 9.59 (0.98), painless-DPN 9.94 (0.97)) this was not statistically significant (p=0.088). However the ΔTTP in response to thermal pain was significantly different between the groups LT (p<0.021), Rt (p=0.003), LSC (p=0.009), RSC (p=0.008). Whilst HV respond to thermal pain by shortening the TTP in ROI the painful-DPN group do the reverse (p<0.05).

Conclusion: Subjects with painful-DPN have a paradoxical increase in TTP, indicating that chronic neuropathic pain state may result in a failure to mount a hemodynamic response to external pain and descending inhibition. This novel finding may serve as an objective marker of painful-DPN, and in the future may facilitate the development of novel treatments.

Supported By: European Foundation for the Study of Diabetes
**COMPLICATIONS—NEUROPATHY**

**569-P**

Amelioration of Peripheral Neuropathy in Mouse Models of Diabetes by Dietary Reversal

PHILIPPE D. O’BRIEN, KAI GUO, LUCY M. HINDER, JOHN M. HAYES, FAYE MENDelson, MAEGAN A. TABBEY, JUNGYUK HUR, EVA L. FELDMAN, ANN ABBOC MD, Grand Forks, ND

Peripheral neuropathy (PN) is a common complication of prediabetes and type 2 diabetes (T2D). Lifestyle changes, including dietary reversal (DR), can reverse PN, although the mechanisms involved remain unclear. The goal of this study was to identify the mechanisms that underlie PN development in prediabetes and T2D and understand which of these are corrected upon DR. To achieve this, we used two models of PN and looked at the effects of DR on global gene expression and lipid profiles in peripheral nerves. C57BL/6J mice were fed a standard diet (10% kcal fat, SD) or high fat diet (60% kcal fat; HF) from 5 weeks. A subset of HF mice were injected with STZ at 12 weeks to induce hyperglycemia, reflecting a more diabetic-like phenotype. At 16 weeks, subsets of HF and HF-STZ mice were placed on the standard diet for 8 weeks (HF-DR and HF-STZ-DR, respectively) until 24 weeks when terminal phenotyping was performed. At baseline and at study completion, sciatic nerve tissue was processed for gene expression by RNAseq or for lipid species profiling by untargeted shotgun lipidomics. HF and HF-STZ mice display PN compared to controls. In contrast, peripheral nerve function of HF-DR and HF-STZ-DR mice was corrected upon DR. Neuronal gene expression analysis revealed numerous differentially expressed genes (DEG) when comparing SD to HF or HF-STZ mice. Interestingly, a proportion of the genes dysregulated in HF and HF-STZ, were similarly reversed by DR. KEGG enrichment of these genes revealed that lipid metabolism pathways were enriched. Lipidomic analysis revealed a similar pattern of differentially altered lipids that were reversed by DR in HF and HF-STZ mouse models. Lipids reversed by DR include diacylglycerol, a known mediator of insulin resistance.

We demonstrated that DR of HF and HF-STZ mice can restore peripheral nerve function. We also show that genes related to lipid function are dysregulated in diseased states and are reversed by DR. This study supports the idea that DR improves peripheral nerve function by restoring lipid homeostasis.

**Supported By:** National Institutes of Health (R01DK082841; R01DK107956); Novo Nordisk Foundation (NNF14SA00106); Program for Neurology Research & Discovery; Milstein, Nathan and Rose Research Fund; Sinai Medical Staff Foundation; A. Alfred Taubman Medical Research Institute

**570-P**

PGC-1α Determines the Formation of Neuronal Respiratory Chain Supercomplexes That Regulate Mitochondrial Function

JOUNGIL CHO, MOHAMMAO SALIMIAN, SAI SRUTHI REDDY KONDURU, JAMES RUSSELL, Baltimore, MD

Loss of PGC-1α signaling is important in the development of experimental diabetic neuropathy (DN) [Choi J et al. Neurobiology of Disease, 2014; 64: 118-133]. In PGC-α knockout (KO) mice there is exacerbation of DN with loss of large and small myelinated fibers, loss of mitochondria (Mit) and DNA content, and increased protein oxidation. We have shown potential important functions of 35-kDa PGC-1α, a novel PGC-1α isoform in regulating Mit integrity. The focus of the present work was to analyze the respiratory chain integrity in neurons of PGC-1α KO mice. In the respiratory supercomplexes of 1,030, 980, and 840 kDa, the levels of complexes 1,030 and 980 kDa are significantly decreased, while the level of 840 kDa complex is significantly increased in PGC-1α KO mice compared to wild type (WT) mice. Mass spectrometry analysis identifies: 1) subunits of complex I, III, and IV in the 1,030-kDa band, 2) subunits of complex I and III in the 980-kDa band, and 3) subunits of complex I in the 840-kDa band. Quantification results reveal that the activities of complexes I, III, and IV within the 1,030-kDa protein complex are significantly decreased in PGC-1α KO mice. In contrast, we observe little complex I, III, and IV activities either in the 840- or 980-kDa complex. We observed altered Mit morphology and impaired respiration in PGC-1α KO mice. Co-immunoprecipitation and mass spectrometry analyses reveal that the 35-kDa PGC-1α is associated with NADH dehydrogenase (ubiquinone) flavoprotein 2 (NDUFV2), a subunit of respiratory complex I in the Mit. Immuno blot analysis combined with two-dimensional-blue native gel show the presence of both 35-kDa PGC-1α and NDUFV2 proteins in the 1,030-kDa protein band. These results are consistent with a cooperative role of 35-kDa PGC-1α and NDUFV2 in the organization of Mit respiratory supercomplex assembly. The study provides evidence that 35-kDa PGC-1α is present in the Mit where it could directly regulate Mit function and affect response to diabetes.

**Supported By:** National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases (R01DK107007-01A1); U.S. Department of Veterans Affairs

**571-P**

Eyecon Is a Novel Diagnostic Tool for Diabetic Neuropathy

MOUFINA BEN NASR, ELENA GIULIANI, FRANCESCA D’AD O, ANNA MAE STRONI, VERA USUELLI, STEFANIA BIANCHI MARZOLI, PAOLO FIORINA, Boston, MA, Milan, Italy

Diabetic neuropathy (DN) is a major complication of diabetes, causing more than 50% of all hospital accesses related to type 1 diabetes (T1D). However, diagnostic criteria are not yet standardized, and diagnosis also of symptomatic DN is often underestimated. Given the medical need for an accurate non-invasive diagnostic tool, we developed a test based on tracking eye movement for early detection of DN called Eyecon. SRLab -Tobi TX300 Eye tracker®, an eye-tracking device, is coupled with a series of screens on a computer to test the velocity and accuracy of gaze movement in healthy controls (CTRL, n=30), T1D patients without neuropathy (T1D, n=19) and T1D patients with neuropathy (T1D-N, n=14). The screens are divided in 5 classes: Resistance, Wideness, Pursuit, Velocity and OKN. They aim to evaluate both smooth and saccadic movement in different directions. We evaluated a total of 483 parameters and observed that 27 (5.6%) were altered in T1D patients without signs of advanced DN at the electromyography as compared to CTRL, while 29 (6%) were altered in T1D-N patients, for a total of 56 (11.8%) significantly altered parameters (T1D vs. CTRL). Our pilot study demonstrated the feasibility of this non-invasive exam and its ability to early detect DN, despite the limitations of a small number of subjects.

**572-P**

The Association between Urinary N-Acetyl-β-D-Glucosaminidase and Cardiovascular Autonomic Neuropathy in Patients with Diabetes

MIN SUN CHOI, JI EUN JIN, KYU YEON HUR, MUN-JU KYU Lee, JAE HYE IN KIM, Seoul, Republic of Korea

Background: Cardiovascular autonomic neuropathy (CAN) is a microvascular complication of diabetes, which involves autonomic nerve fibers innervating the heart and vessels, resulting in increased cardiovascular morbidity and mortality. Previous studies reported that diabetic CAN is related to microalbuminuria. However, it is unclear whether CAN is related with urinary N-acetyl-β-D-glucosaminidase (uNAG), which was suggested as an early marker of renal tubular injury in diabetic nephropathy recently.

Methods: Cross-sectional data of 1052 patients with diabetes were analyzed who had tests for uNAG and autonomic function test at outpatient clinic. The presence and severity of CAN were assessed by the five autonomic function tests.

Results: The association between uNAG and the presence of CAN in patients with type 1 diabetes (T1D) (n=161) was significant in multivariate analysis (DR 1.20, 95% CI 1.03-39; p = 0.018) after correction of variables including age, duration of diabetes, glyceric index and albuminuria, but it was insignificant in patients with type 2 diabetes (T2D) (n=881). Among quartile groups divided by uNAG levels, prevalence of CAN was significantly increased across with higher quartiles of uNAG level only in patients with T1D (p = 0.013). The association between uNAG and the total CAN score, assessed as the severity of CAN, was significant in both patients with T1D (p = 0.033) and T2D (p = 0.006) in multivariate analysis (OR 1.20, 95% CI 1.03-39; p = 0.018).

Conclusion: Elevated uNAG is associated with the prevalence of CAN only in patients with T1D, and it is also related to the severity of CAN in both patients with T1D and T2D. It suggests that elevated uNAG might be a potential marker for the development and progression of CAN in patients with diabetes.

**573-P**

Monounsaturated Fatty Acids Prevent Saturated Fatty Acid-Induced Impairment of Mitochondrial Trafficking in Dorsal Root Ganglion Sensory Neurons

AMY RUMORA, GIOVANNI LOGRASSO, JULIA A. HAIDAR, JUSTIN DOLKOWSKI, STEFANIA BIANCHI MARZOLI, PAOLO FIORINA, STEPHEN I. LENTZ, EVA L. FELDMAN, Ann Arbor, MI

Diabetic neuropathy (DN) is a common complication of type 2 diabetes characterized by peripheral nerve damage and sensory loss. Dorsal root ganglion (DRG) sensory neurons require axonal mitochondrial transport to produce axonal ATP for neuronal function. In DN, DRG neurons exhibit axonal mitochondrial dysfunction and bioenergetic failure. A correlation between DN progression and dyslipidemia suggests that increased plasma saturated fatty acids (SFA) and decreased unsaturated SFA may play a role in the progression of DN. In this study, we evaluated the effect of saturated FA palmitate and monounsaturated FA oleate on mitochondrial trafficking and mitochondrial function in DRG neurons. Primary DRG neurons were treated with physiological concentrations of palmitate, oleate, and oleate/palmitate
Comparison of Cognitive Function, Depression, and Sleep Quality among Type 2 Diabetes Mellitus Patients With and Without Diabetic Neuropathy

CHANDRAI RATHAKRISHNAN, RNIN R. CR, SREEJITH K, ANJUSHI UT, Manoj, India, Kerala, India

Diabetic neuropathy is one of the most common complications of diabetes mellitus. Many studies had reported that type 2 diabetes mellitus increases the risk of cognitive impairment, depression, and sleep impairment in patients with diabetes mellitus. The main objective of the study is to determine whether any significant impairment in cognition function, sleep quality, and depression status exist among diabetic neuropathy patients compared to patients with type 2 diabetes mellitus alone. A prospective observational study was conducted in a tertiary care teaching hospital. Patients who satisfied both inclusion and exclusion criteria were included in the study. A total of 93 type 2 diabetes mellitus patients with neuropathy and 55 patients with out neuropathy were enrolled in to the study after obtaining written informed consent. Cognitive status was assessed with the help of MOCA questionnaire. Sleep quality was assessed by using Pittsburgh sleep quality index questionnaire and depression, by using PHQ-9 questionnaire. The diabetic neuropathic patients showed a significant impairment in cognitive status (P value 0.003), sleep quality (P value 0.000) and depression status (P value 0.000). The study concluded that diabetic neuropathy increases the risk of cognitive impairment, impairment in sleep quality and depression in type 2 diabetes mellitus patients.

Suppression of Neuropathy Development in Diabetic Rage-Deficient Mice Is Associated with Absence of M1/M2 Macrophage Skewin

SHO OSGOOD, HIROKI MIYAKAWA, SADORI OASAWARA, KAZUISHI TAKAHASHI, KAZUNORI SANO, SOROKU YAGIHASHI, Hiramine, Japan, Tokyo, Japan

Infiltrating macrophage (Mφ) into sciatic nerve (SN) is assumed one of the pathogenesis of diabetic polyneuropathy (DPN). In particular, skewing infiltrating Mφ toward pro-inflammatory (M1) Mφ but not anti-inflammatory (M2) Mφ, possibly contributes to dysfunction of SN in diabetic state. However, the impacts of Mφ into dorsal root ganglia (DRG) in DPN are not yet well explored. For this purpose, male C57Bl/6 mice (W) and receptor for AGEs (RAGE) null mice (R) were recruited and rendered diabetic (D) with STZ injection. After 8 weeks, nerve conduction velocity (NCV) and tail flick test were performed. Subsequently, mice were sacrificed to dissect SN and DRG, in order to observe the changes. Staining of S100β, GFAP, and CD68 were carried out to examine the glial and inflammatory cells. The results indicated that M1/M2 macrophage skewing in diabetic rats has no significant effect on the number of M1/M2 macrophages in SN and DRG. The results of the study showed that the changes in large fiber function accompany the loss of small nerve fibers and occurs in patients with T2DM already in the preclinical stage of DPN. CCM can be a powerful tool for non-invasive early diagnosis of neuropathy in subclinical stage DPN.
578-P Cardiovascular Autonomic Neuropathy and Uric Acid in Subjects with Type 1 Diabetes—Preventing Early Renal Loss (PERL) in Type 1 Diabetes Trial
MAMTA JAIWAL, ALESSANDRO DORIA, MICHAEL MAUER, RODICA POP-BUSUI, Ann Arbor; MI, Boston, MA; Minneapolis, MN
Elevated serum uric acid (SUA) is an established risk factor for diabetic nephropathy (DN) may also be a risk factor for cardiovascular autonomic neuropathy (CAN). We evaluated the cross-sectional association between CAN and SUA levels in subjects with type 1 diabetes (T1D), mild to moderate chronic kidney disease (CKD) and a SUA ≥ 4.5 mg/dL enrolled in the ongoing PERL trial that is evaluating the effect of SUA lowering by allopurinol on kidney function decline, specifically iohexol plasma disappearance glomerular filtration rate (iGFR). Also measured are estimated GFR (eGFR) and albumin excretion rates (AER). Measures of baseline CAN included resting heart rate, standard deviation of normal RR interval (SDNN), and QT (Bazzett formula) derived from resting ECG recordings (RR interval extracted from digital ECG images by ECGSCAN software). Four hundred ninety seven PERL participants had valid baseline CAN and renal function data (age 51 ± 11 years, 66% male, T1D duration 35 ± 12 years, HbA1c 8±1%). Subjects in the highest tertile of serum UA levels had worse measures of renal function [GFR 60 ± 16 vs. 74 ± 60 ml/min/1.73 m²; GFR 85.7 ± 18 vs. 82.7 ± 17.2 ml/min/1.73 m²; AER 370 ± 783 vs. 1181 ± 475 mcg/mg creatinine] compared to those in the lowest tertile. SDNN correlated negatively with SUA levels (β = -0.01; P = 0.003). In a multiple linear regression model, lower SDNN was associated with higher SUA levels independent of age, gender, BMI, blood pressure, and HbA1c (β = -0.061, SE = 0.021, P = 0.0049), but this association was no longer significant when adjusted for GFR (β = -0.0184, SE = 0.024, P = 0.46). In summary, elevated SUA was significantly associated with CAN in subjects with T1D independent of some traditional cardiovascular risk factors. This relationship operated, at least in part, through the inverse association of SUA levels with renal function.

Supported By: American Diabetes Association (1-16-PDF-051) to M.J.; National Institute of Diabetes and Digestive and Kidney Diseases (1UC4 K01108)

579-P Impaired Baroreflex Sensitivity in Patients with Recent-Onset Type 2 Diabetes
GIDDON J. BÖNHOF, ALEXANDER STROM, KÄLMAN BÖDIS, KARSTEN MÜSßIG, JULIA SZENDROEDI, MICHAEL RODEN, DAN ZIEGLER, Düsseldorf, Germany
Impaired baroreflex sensitivity (BRS) is a sign of diabetic cardiovascular autonomic neuropathy (CAN) which often remains undiscovered during the early course of diabetes. We aimed to determine whether BRS alterations can be detected in patients with recent-onset type 1 and type 2 diabetes. Continuous plethysmographic arterial pressure and R-R intervals were recorded using the Finometer (Finapres Medical Systems) from the left middle finger in 586 participants from the baseline German Diabetes Study (GDS) cohort with type 1 or type 2 diabetes and a known diabetes duration ≤1 year (T1D/T2D [mean±SD]: 209±578; age: 34.7±11.5/51.6±10.3 years; male: 60/74%; BMI: 24.7±4.2/31.6±3.6 kg/m²; diabetes duration: 3.6±3.3/9.3±5.9 months; HbA1c: 6.5±1.8/8.0±0.9% and corresponding controls [CON1/CON2: n=74/208; age: 36.4±10.4/4.14±8.8 years; male: 64/64%; BMI: 26.5±4.9/26.6±4.8 kg/m²; HbA1c: 5.2±0.3/5.3±0.3%]. BRS parameters included the alpha index of spectral power (BRSα), transfer function cross spectrum (BRSseq), and sequence analyses (BRSseq). After adjustment for sex, age, BMI, and smoking, all three BRS measures were reduced in T2D vs. CON2 (BRSα: 10.1±8.6 vs. 15.4±12.2 ms/mmHg; BRSseq: 8.7±5.9 vs. 10.4±3.5 ms/mmHg; BRSseq: 9.85±0.07 vs. 13.3±6.6 ms/mmHg [P≤0.01], while no such differences were observed in T1D vs. CON1. Multiple regression analyses revealed, that systolic blood pressure (SBP) was the strongest determinant of lower BRS in T2D [BRSseq/BRSα/BRSβ: β=−0.32/−0.23/−0.23] followed by age (xQRS: β=−0.18) and lower HDL cholesterol (BRSseq: β=-0.23), while in T1D it was age [BRSseq/BRSα/BRSβ: β=-0.37/−0.38/−0.34] SBP [xQRS/BRSα/BRSβ: β=-0.26], and BMI [BRSseq: β=-0.24] (all P<0.01). In conclusion, reduced baroreflex sensitivity indicates early CAN in recent-onset type 2 diabetes in relation to modifiable risk factors such as higher systolic blood pressure and lower HDL cholesterol.

Supported By: German Ministry of Culture and Science of the State of North Rhine-Westphalia; German Federal Ministry of Health; German Federal Ministry of Education and Research

580-P The Reference Distribution of Annual Change in Corneal Nerve Fibre Length in Diabetes Mellitus
EVAN J.H. LEWIS, MITRA TAYAKOLL, LEIF ERIK LOWBLOM, ELISE M. HALPERN, MARIA JEZIORSKA, DANIELE PAPAUD, NICOLA FRITIARD, RUNI M. SHTEIN, NATHAN EFRON, VERA BRIL, RAYAZ A. MALIK, BRUCE A. PERKINS, Toronto, ON; Caniaba, East: United Kingdom; Manchester, United Kingdom; Calgary, AB; Canada; Brisbane, Australia; Ann Arbor, MI, Doha, Qatar
The measurement of corneal nerve fibre length (CNFL) by in vivo corneal confocal microscopy is a biomarker for the presence of diabetic sensorimotor peripheral polyneuropathy (DSP). We aimed to determine the reference distribution of annual CNFL change, its prevalence in T1D and T2D, and its clinical predictors. We examined longitudinal data from 94 non-diabetic controls and 297 diabetes patients (224 T1D and 73 T2D) from an ongoing multi-centre NIH-funded study of IVCMC in diabetes. Patients were included if they had at least 1-year of follow-up data and were classified as progressors with "rapid corneal nerve fibre loss" (RCNFL) if the loss of CNFL was beyond the 5th percentile by age, sex, BMI, HbA1c or CNFL levels. Nonprogressors were 43.0±15.8 y, had a median of 2 follow-up visits over a median of 2 y, baseline CNFL of 15.4±2.7 mm/mm², and the median annual change in CNFL was -1.7%/90% CI, -14.3 to 30.9%. Diabetes patients were 49.6±15.5 y, had a median of 3 visits over a median of 2 y, baseline CNFL of 14.3±4.4 mm/mm² and the median annual change in CNFL was 1.9%/90% CI, -26.1 to 25.0%. There were 33 (3.1%) cases of RCNFL in the diabetes subcohort, which was comparable between T2D (11.0%) and T2D (79.9%). Progressors did not differ from non-progressors for baseline levels of age, sex, BMI, HbA1c or CNFL levels. However, progressors were more likely to have baseline DSP (10/50%) vs. 8/32% (p=0.048), lower cooling detection threshold (21.3±3.8 vs. 25.3±4.2, p=0.048) and lower heart rate variability (26.3±13.3 vs. 38.2±25.4, p=0.036). A more rapid loss of CNFL (RCNFL exceeding 14%/y) occurs in ~11% of diabetes patients. This more rapid of corneal nerves may identify patients at highest risk for the development or progression of DSP.

Supported By: National Institutes of Health; JDRF

581-P Mast Cell Precursors and Diabetic Neuropathy—Is Immunity the Connection?
MARIA SAMBATARO, LUISA SAMBADO, ENRICA TREVISIOL, AGOSTINO PAC-CAGNELLA, Castelfranco Veneto, Italy; Treviglio, Italy
Introduction: Diabetic neuropathy and distal foot lesions are common complications of type two diabetic patients (T2DM), however the underlying pathophysiology remains uncertain. Mast cells (MCs) provide a possible link with immunity and neuroinflammation. These cells of innate immune system are found near sensory nerves or the endoneurial compartment, where they differentiate and participate in innate host defense reactions. MCs are involved in wound healing, but their role in diabetes is unknown. Aim: To evaluate a possible connection between peripheral bone marrow derived blood MC precursors and diabetic neuropathy without and with ischemic skin lesions.

Methods: We enrolled 26 healthy controls (C), 15 T2DM with peripheral sensorimotor neuropathy (N) and 14 T2DM with neuropathy, distal ischemia (allux ischemia <30 mm Hg) and foot lesions (N1). Peripheral blood was analyzed by flow-cytometry (CD34, CD117, lineage cocktail 1 and FcεRI antibodies).

Results: We found a significant decrease of MC precursors (LIN-; CD34+, CD117+, FcεRI+ cells) in N and N1 (0.0008 and 0.00051% of mononuclear cells vs. 0.0018% in C, p<0.04). MC number directly correlated with total lymphocyte (p=0.005, R=0.474) T-lymphocyte (p=0.005, R=0.396) and CD4+ T-lymphocyte (p=0.014, R=0.515) numbers. There was an inverse but not significant correlation with monocytes (p=0.073, R=0.197).

Conclusions: Our results show a possible involvement of MC precursors in human neuropathy and neuroischemic diabetic foot lesions. Conceivably, MCs could have a protective role in favoring wound healing by interaction with cells such as fibroblasts, endothelial, immune, nervous and epithelial cells and by release mediators and neurotransmitters. The correlation with T-lymphocytes might explain the impaired wound healing in N1, suggesting a direct contact between the two populations at the lesion site. Although not significant, the inverse relation with monocytes could be up-regulated by the decrease in MC precursors.
Clinical Application of Photoacoustic Imaging to the Evaluation of Diabetic Polyneuropathy
SOROKU YAGIHASHI, Chiba, Japan

Objective evaluation of peripheral nerve function and pathology is essential for the early diagnosis and determination of clinical staging of diabetic polyneuropathy (DPN). To this end, we attempted to apply the photoacoustic imaging (PAI) to clinical diagnosis of DPN and characterization of background pathology. PAI is the imaging system for the dual ultrasound detection of the specific tissues or organs and released signals from the same tissues irradiated with laser light with specific wave length. For the application of PAI to DPN, we selected the median (MN) and sural nerves (SN) for the evaluation and applied laser light to these nerves for the detection of signals from hemoglobin. With this method, PAI enables depiction of nerve bundle cross sectional area (NCA), and hemoglobin distribution, thereby blood volume (BV), vascular area (VA) or caliber at the arteriolar/venular levels. In this study, 12 healthy control subjects (C) and 54 diabetic patients (DM) with (n=30) or without DPN (n=24) were subjected to PAI examination. DPN was confirmed by Japanese study group criteria. Correlation analysis was also conducted between PAI data and clinical staging of DPN. We found significant increases of NA 14% in MN and 19% in SN in DM compared to C, and trends of increases of NA toward advanced DPN. There was also a trend of increase in VA in DM with advanced DPN although there was no significant difference between C and DM. Compared to C, BV in SN was increased 12% in DM, but it was decreased in DM with DPN compared to those without DPN. These findings indicated that expanded nerve bundle area with decreased BV was characteristic in DPN. Our results suggest that endoneurial edema of nerve bundles, epi- and perineurial fibrosis and congestion with endoneurial ischemia may contribute to the development of DPN. We consider that PAI is a new and valuable method for the clinical application to DPN.

Supported By: Japan Ministry of Education, Culture, Sports, Science and Technology

Altman in Histone Acetylation in Diabetic Painful Neuropathy
MUNMUN CHATTOPADHYAY, VIKRAM THAKUR, El Paso, TX

Peripheral sensory neuropathy is one of the most common complications of diabetes. Accumulating evidence suggests that chronic low-grade inflammation is involved in the pathogenesis of the disease. We hypothesize that hyperglycemia causes changes in histone acetylation and release of inflammatory mediators in the peripheral nervous system of diabetic animals with painful neuropathy; therefore blocking this increase will prevent or delay the development of neuropathy. High mobility group box 1 (HMGB1), a nuclear protein released by injured and severely stressed cells, promotes cytokine release via histone acetylation and its interaction with the Toll-like receptor (TLR). In this study we investigated the changes in inflammatory mediators, including HMGB1, TLR4 and H3K9 acetylation as determined by the photoacoustic microscopy (PAIM) approach for this difficult-to-treat complication of diabetes.

Type 2 diabetic (T2D) animals with pain were treated with HMGB1 inhibitor Glycyrrhizin (GLC) for 2 days a week for 3 weeks at 50 mg/kg IP injection 6 weeks after diabetes. T2D animals demonstrated significant changes in thermal hyperalgesia manifested by a decrease in withdrawal latency to heat, mechanical hyperalgesia as measured by the Randall-Selitto method of paw pressure at 6 weeks after diabetes and also exhibited marked increases in HMGB1, TLR4 and H3K9 acetylation as determined by the Western blot analysis and immunohistochemistry. We analyzed the T2D animals with treatment or without treatment at 3 weeks after treatment. Our results show that animals treated with GLC had significant decrease in thermal hyperalgesia along with changes in histone acetylation and expression of inflammatory mediators. This preliminary study suggests that HMGB1 and histone acetylation play an important role in the inflammatory aspect of the painful neuropathy in T1D animals and may provide a novel treatment approach for this difficult-to-treat complication of diabetes.

Supported By: American Diabetes Association (1-12-DS-021 to M.C.), Texas Tech University Health Sciences Center

Insulin Resistance, Cardiovascular Autonomic Neuropathy, and Left Ventricular Hypertrophy in Patients with Congenital Generalized Lipodystrophy
VIRGINIA D. FERNANDES, CLARISSE M.M. PONTE, MARIA HELANE C. GURGEL, ANA PAULA D.R. MONTENEGRO, LIVIA A.A. BATISTA, CRISTIANE B.R. LIBERATO, CATARINA B. D'ALVA, RENAN M. MONTENEGRO, JR., BRAZILIAN LIPODYSTROPHY STUDY GROUP (BRAZILPO), Fortaleza, Brazil

Congenital generalized lipodystrophy (CGL) subjects have a high prevalence of cardiovascular autonomic neuropathy (CAN) and cardiac complications, including left ventricular hypertrophy (LVH). This study aimed to analyze insulin resistance (IR), CAN severity and LVH association. A cross sectional study with 10 CGL patients and 20 healthy controls. We evaluated clinical and laboratory data, echocardiogram parameters, 3 spectral analysis components, high frequency (HF), low frequency (LF), and very low frequency (VLF), of heart rate variability (HRV), sympathetic-vagal balance, time domains of HRV, corrected QT interval (cQT), and 4 cardiovascular reflexes tests (postural hypotension test, orthostatic, respiratory, and vasalva coefficients - 2 abnormal tests: clinic CAN, 1 abnormal test: incipient CAN, and postural hypotension: advanced CAN). In CGL group 50% had CAN (40% clinic and 10% incipient) and 40% LVH. There was inverse correlation between LVMI and HF (r=0,007), IVS and HF (p=0,013), and positive correlation between IVS and HOME-IR (r=p=0,042), and BP drop (p=0,010). These suggest that IR may be involved in the severity of CAN and cardiac autonomic dysfunction in the pathophysiology of cardiovascular complications in these disease.

Table.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CGL group (n=10)</th>
<th>Control group (n=10)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>12.6 (2.0)</td>
<td>12.3 (2.1)</td>
<td>0.642</td>
</tr>
<tr>
<td>BMI</td>
<td>30.9 (5.8)</td>
<td>25.8 (4.1)</td>
<td>0.000</td>
</tr>
<tr>
<td>Body mass index (BMI)</td>
<td>19 (2.9, 23.8)</td>
<td>17.2 (14.4, 24.8)</td>
<td>0.257</td>
</tr>
<tr>
<td>Glycemia (HbA1c %)</td>
<td>7.3 (7)</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td>Fasting blood sugar (mg/dL)</td>
<td>100 (100)</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>199 (67)</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>50 (10)</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td>CAN % (n)</td>
<td>55 (5)</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td>CAN (n)</td>
<td>4 (4)</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td>Incontinent CAN % (n)</td>
<td>10 (10)</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td>LVMI % (n)</td>
<td>43 (43)</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td>LVMI (g/m2)</td>
<td>50.9 (26.1)</td>
<td>25.7 (15.5)</td>
<td>0.000</td>
</tr>
<tr>
<td>IVS (mm)</td>
<td>0.4 (0.1)</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td>LVPW (mm)</td>
<td>1.5 (0.3)</td>
<td>0</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Supported By: American Diabetes Association (R-12-DS-021 to M.C.), Texas Tech University Health Sciences Center

WITHDRAWN

Supported By: ADA-Supported Research
thought you moved to the left and the button in your right hand if you thought by a helmet. The platform repeatedly exposed subjects to small motions and the subject sitting in a chair on a moving platform with the head held firmly blood sugar control (HbA1c: 6.8, 9.1, 13 and 7.6). Thresholds were tested with and 17 years before testing. Subjects were not screened for neuropathy or 52-69, one female) who received a diagnosis of type 2 diabetes between 12 We selected this approach because thresholds are sensitive to pathology, vestibular perceptual thresholds in subjects with type 2 diabetes. These individuals with diabetes have increased postural sway and risk of falling. Many systems, and sensory feedback about body motion plays a critical role. Indi-
able C-peptide levels had lower rates of these complications (33.3% vs. 58.1%, p=0.045). This association remained significant in logistic regression after controlling for duration of diabetes and HbA1c with a statistically significant odds ratio of 0.39 (95% CI: 0.89-0.94). When those with neuropathy were added to the overall microvascular complication group, no significant differences were found (p=0.13). These findings are consistent with the hypothesis that proliferative retinopathy and possibly nephropathy in T1D may be influenced by persistent C-peptide secretion.

Supported By: National Institutes of Health (DK64810) Rossi Memorial Fund

500-P

Neutrophil Elastase Contributes to the Early Molecular Abnormalities of the Retina in Diabetest

HAI TAO LIU, TIMOTHY KERN, Cleveland, OH

Introduction: Previous studies by our lab indicate that neutrophils are involved with capillary degeneration in diabetic retinopathy (DR). The elastase is a serine protease in neutrophils that plays an important role in a variety of inflammatory diseases, such as chronic obstructive pulmonary disease. We are investigating the potential role of NE in the development of DR.

Method: The activity of neutrophil elastase (NE) was selectively inhibited (by daily sivelestat) or deleted (Elane-/-) from diabetic mice, and the effects of NE loss were compared to the effects of inhibition of general protease activity (over-expression of protease inhibitor, alpha-1 antitrypsin). Molecular abnormalities associated with the development of DR, including retinal superoxide production, expression of proteins associated with inflammation, and leukocyte-mediated cytotoxicity of retinal endothelial cells were used to determine the effects of NE in diabetic mice.

Result: At two months of diabetes, selective inhibition of NE or deletion of the elastase both inhibited diabetes-induced superoxide production and inflammation in the retina. Both also inhibited leukostasis and/or leukocyte mediated damage to endothelial cells in cell cytotoxicity assays. In contrast, over-expression of alpha-1 antitrypsin resulted in increased retinal superoxide production and leukocyte activity in cytotoxicity assays in both diabetic and nondiabetic animals.

Conclusion: NE may play an important role in the development of DR.

Supported By: National Institutes of Health (EY022938, R24EY024884)

501-P

Anemia as a Risk Factor for Diabetic Retinopathy (DR) with Special Reference to Nutritional Etiology

JYOTHI IDICULLA, SUNEETHA NITHYANANDAM, MARY JOSEPH, CHRISTEENA J., Bangalore, India

Background: Anemia is increasingly recognized as a risk factor for DR. Nutritional anemia is a major cause of anemia in India. This study was undertaken to explore anemia as a risk factor for DR.

Methodology: Patients with type 2 diabetes admitted to the medical wards of a tertiary care hospital were enrolled into the study, in the absence of renal failure, pregnancy and ocular disorders unrelated to diabetes. Retinopathy was classified as per ETDRS classification. Anemia was defined and graded based on WHO guidelines. In patients with anemia, serum B12, serum iron, total iron binding capacity (TIBC) and percent saturation were assayed.

Results: A total of 170 patients were enrolled into the study (males 93, females 77). The mean age of the study group was 59 ± 12.30 (SD) years. Patients with DR (n=85) were classified as Group 1 and those without DR (n=85) as Group 2. The mean age of patients in Group 1 was 60.74 ± 13.00 (SD) years and that in Group 2 was 57.26 ± 11.39 (SD) years. The mean Hb of patients in Group 1 was 10.40 ± 0.25 (SD) gm% and in Group 2 was 10.17 ± 0.30 (SD) gm%. The incidence of anemia (iron: 24, B12: 3 and dual: 1). On logistic regression analysis, anemia association between anemia and DR (p=0.001) and a trend towards association between increasing grades of anemia and severity of DR (p=0.08). In Group 1, among patients with anemia, 28 (50%) patients had nutritional anemia (iron: 24, B12: 3 and dual: 1). On logistic regression analysis, anemia and duration of diabetes were predictors of DR. Anemia in patients with diabetes may be multifactorial in etiology. While metformin therapy, albuminuria and reduced renal function are implicated, vegetarian diet is a major contributor for nutritional anemia. Regular monitoring of Hb and treatment with supplements or dietary modifications may reduce occurrence and arrest progression of DR.

Supported By: Department of Health (EJO22938, R24EY024884)

502-P

Angiotensin-(1-7) Attenuates Protein O-GlcNAcylation in the Retina of Mice Fed a High-Fat Diet

SADIE DIERSCHKE, AMY C. ARNOLD, ALISTAIR J. BARBER, MICHAEL D. DENNIS, Hershey, PA

Increased retinal protein O-GlcNAcylation occurs in response to hyperglycemia and contributes to diabetic retinopathy (DR). Alternatively, systemic pharmacological blockade of the Renin-Angiotensin System (RAS) lowers the incidence of DR. The classic RAS that systemically regulates blood pressure is defined by the ACE/AT1R/AT1 axis; this is counter-regulated by actions of the ACE2/Angiotensin-(1-7)/Ang(1-7)/Mas axis of the RAS. Increased endogenous production of Ang1-7 is responsible for many of the beneficial effects of cardio protective RAS blockers such as ACE inhibitors; however the mechanism whereby DR outcomes are improved remains unresolved. The hypothesis here is that Ang1-7 acts to reduce retinal O-GlcNAcylation by activating Protein Kinase A (PKA) and thereby inhibiting the rate-limiting enzyme of the hexosamine biosynthetic pathway, glutamine-fructose-6-phosphate amidotransferase (GAFAT). Mice fed a 60% high fat diet (HFD) for 11 weeks and treated with the ACE inhibitor captopril (50 mg/L) for 3 weeks exhibited a Mas receptor-dependent attenuation of retinal protein O-GlcNAcylation as compared to vehicle treated controls. To determine the mechanism by which Ang1-7 regulates O-GlcNAcylation, R28 retinal neurons were treated with Ang1-7 and the adenylyl cyclase activator forskolin. Both Ang1-7 and forskolin increased cAMP concentrations and attenuated levels of protein O-GlcNAcylation induced by treatment with the O-GlcNAcase inhibitor thioglycolate. Conversely, CAMP activates PKA, which phosphorylates and inhibits GAFAT. Overall, these studies establish the first link between dysregulation of the well-studied physiological RAS and diabetes-induced retinal tissue damage — as a consequence of excessive protein O-GlcNAcylation.

Supported By: American Diabetes Association/Pathway to Stop Diabetes (1-14-01-04 to M.D.D.)

503-P

Abnormal Electoretinography in Patients with Long-Duration Diabetes but No Retinopathy

BELINDA BROOKS, DENNIS YUE, ELLEN LANDY, YI SHI, Camperdown, Australia, Sydney, Australia

Retinopathy increases with duration of diabetes but the presence of this microvascular complication in individual patients remains unpredictable. Retinal neurophysiological changes have been postulated to be important in modulating susceptibility. We performed electroretinography (ERG) on patients with long duration of diabetes (>15 years) but no retinopathy to determine whether this setting of “normal retinal morphology” is also characterised by normal electrophysiology of the eyes. ERG was performed with a handheld RE-100 device. Flirering lights at 30Hz was used to stimulate retinal electrical activity recorded by skin electrodes placed below the lower eye lids. Implicit time (electrical conduction time, msec), amplitude (uV) and pupil diameter (mm) were recorded. A composite score < 20 of these three parameters indicates a <1% risk of vision threatening retinopathy. Altogether 26 type 2 and 9 type 1 patients with no retinopathy but diabetes duration ≥22.5±4.5 and ≥32.8±4.4 years respectively were studied. Nondiabetic individuals (fasting BGL<6.0mM or HbA1c<6.0%) n=25 acted as controls. Results in Table 1 showed the implicit time of individudals with diabetes but no retinopathy was minimally increased but the amplitude was significantly reduced by ~30% (p<0.01). We conclude that the eyes of these patients protected from diabetic retinopathy nevertheless showed retinal neural dysfunction.

Table 1. Electoretinographic findings of patients with long duration of diabetes but no retinopathy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n=25)</th>
<th>T1D (n=34)</th>
<th>T2D (n=34)</th>
<th>T2D-T1D (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of Re/Tiel Test (yrs)</td>
<td>46±9±11</td>
<td>46±10±14</td>
<td>67±11±14</td>
<td>63±10±11</td>
</tr>
<tr>
<td>Gender (Diabetes, yrs)</td>
<td>5±0±2</td>
<td>11±14</td>
<td>13±15</td>
<td>10±15 ±14</td>
</tr>
<tr>
<td>Duration of diabetes (yrs)</td>
<td>5±9</td>
<td>32±6</td>
<td>22±6</td>
<td>25±7 ±14</td>
</tr>
<tr>
<td>B1A1c (%)</td>
<td>5±5±2</td>
<td>7±1±1</td>
<td>7±4±1</td>
<td>7±4 ±1</td>
</tr>
<tr>
<td>Composite Score</td>
<td>68±3±2</td>
<td>31±2±2</td>
<td>21±2±1</td>
<td>33±7 ±15</td>
</tr>
<tr>
<td>Implicit Time (msec)</td>
<td>29±6±2</td>
<td>25±6</td>
<td>23±6</td>
<td>33±7 ±15</td>
</tr>
<tr>
<td>Amplitude (uV)</td>
<td>3±1±2</td>
<td>2±1±2</td>
<td>1±1±2</td>
<td>2±1 ±2</td>
</tr>
<tr>
<td>Pupil Area Rino (mm)</td>
<td>2±0±1</td>
<td>2±0±1</td>
<td>1±0±1</td>
<td>2±0±1 ±2</td>
</tr>
</tbody>
</table>

Different from Control, *p<0.01, **p<0.05, t-test
Are Predictive of Treatment-Required Eye Diseases in Japanese Patients with Diabetes Mellitus

MASAKIHI YAMAMOTO, KAZUYA FUJIIHARA, TAKAO OSUMA, MAVUKO HARADA, MASAIRO ISHIZAWA, HAJIME ISHIKAWA, HIROYUKI SUZUKI, HIROYASU SEIDA, NAOTA YAMANAKA, YASHUSHI MASUBA, HIROYASU SEIDA, NAOTARO YAMANAKA, YASUHIRO MATSUBAYASHI, HIROHITO SONE, Niigata, Japan, Tokyo, Japan

Proteiniuria or low eGFR was separately shown to be associated with the development of retinopathy in patients with diabetes. However, it remains unclear whether semi-quantitatively assessed proteiniuria by test strips either combined or not combined with low eGFR is predictive of incident retinopathy, especially in its advanced stages. To clarify this, we utilized ICD-10 and medical treatment codes from a nationwide claims database that included 6,100 participants (1,074 women, mean age 49.3 ± 9.2 years, eGFR 60 ± 25 mL/min/1.73 m², HbA1c 7.4 ± 1.3%, defined as <45 mL/min/1.73 m²) were used to identify predictors of TRDED during the study period. Among 147 patients developed TRDED, 45 (51%) were female. Cox analysis showed that proteiniuria was a significant and independent predictor of TRDED but not the serum creatinine level. Hazard ratios (HRs) for proteiniuria, low eGFR (defined as <90 mL/min/1.73m²) and HbA1c (per 1% increase) for incident TRDED were 2.37 (95% CI, 1.59-3.53), 3.95 (1.56-10.01), and 1.73 (1.55-1.94), respectively. Compared with participants with neither proteiniuria nor low eGFR, those with proteiniuria but not low eGFR and those with both proteiniuria and low eGFR had 2.2 (1.46-3.34) and 13.2(5.30-34.71), respectively, times higher risk for TRDED. These results implied that proteiniuria worked synergistically with low eGFR but the interaction was not statistically significant. These findings demonstrated that semi-quantitatively assessed proteiniuria using test strips is quick and useful for assessing the risk of development of advanced retinopathy especially in combination with reduced eGFR.

Statins Decrease VEGF Expression in Retinal Pigment Epithelial Cells by Downregulation of Receptor for AGE (RAGE)

HIROKI TSUNUKA, ASASKO ITAYA-HIRANOA, AKIYO YAMAUCHI, SUIMIYO SAKURAMOTO-TsUSCHIDA, MAI MAKINO, RYOGO SHOBATAKE, NAOJUNI MASUDA, HIROMASA HIRAI, NAOHKO OGATA, SHIN TAKASAWA, Kashiwa, Japan

Age-related macular degeneration (AMD) is one of the most important causes of blindness in the elderly patients. Statins, inhibitors for HMG-CoA reductase, are recently reported to be useful for decreasing the risk of wet-type AMD. However, the molecular mechanisms how statins reduce the risk of AMD remain unclear. In this study, we examined the effects of statins (atorvastatin and lovastatin) on the expression of VEGF and RAGE in human retinal pigment epithelial (RPE) cells. We used hIRPE7, human RPE cells, damaged by 20 µM hydroquinone (HQ) +300 µg/mL advanced glycation end-product (AGE) as an experimental AMD model. These cells were treated with atorvastatin (100 nM) or lovastatin (2 µM) for 24 hours. After the treatment, the expression of VEGF and RAGE was evaluated by real-time RT-PCR, and the RT-PCR results showed that the RAGE expression in the statin-treated cells was regulated at the transcriptional level, and that the VEGF expression in these cells was regulated by a post-transcriptional mechanism. These results indicate that statins attenuated the HQAGE-induced VEGF expression via decreasing RAGE expression. As VEGF is an important factor for the development of wet-type AMD, statins could decrease the risk of wet-type AMD and be a preventive medicine for diabetic patients.

Screening for Diabetic Retinopathy in African Immigrants in the Americas

PANOS G. CHRISTAKIS, JEAN DAMASCENE KABAKAMBIRA, SARA M. BRIKER, CHRISTOPHER DUBOSE, ANNE E. SUMNER, EMILY CHEW, Bethesda, MD

The degree to which retinopathy occurs in Africans with abnormal glucose tolerance is unknown. Therefore, the objective of this study was to screen for diabetic retinopathy in self-identified healthy African immigrants. A total of 167 Africans now living in the Washington DC area underwent a medical workup and eye exam at the NIH. Visual acuity, intraocular pressure, slit lamp biomicroscopy and dilated fundus biomicroscopy were performed. Diagnostic testing included color fundus photography, fundus autofluorescence, and optical coherence tomography of the macula and optic nerve. The participants were 41 ± 10 years old (mean ±SD) and duration of stay in the U.S.A was 12 ± 10y. BMI was 26 ± 4 kg/m², and 17 (10%) participants were being treated for hypertension. OGTT revealed diabetes in 15 (9%) participants, and prediabetes in 58 (35%) participants. Retinopathy was detected in 7 (4.2%) participants, 5 of whom had findings consistent with mild non-proliferative diabetic retinopathy in the setting of diabetes (n=3) or prediabetes (n=2) on OGTT. One participant had a flame shaped hemorrhage due to untreated Stage 2 hypertension, and one participant without retinopathy who had peripheral dot-blot hemorrhages. Participants with retinopathy were older (49 ± 10 vs. 40 ± 10 years old, p=0.02), had higher systolic BP (140 ± 25 vs. 119 ± 14 mmHg, p=0.001) and higher AIC (6.4 ± 2.2% vs. 5.4 ± 0.6%, p<0.001) than participants without retinopathy. There was no difference in retinopathy rates based on sex, African region, BMI, education level, income, drinking/smoking status, physical activity, or sickle cell/ HbC trait status. In short, OGTT testing reveals that African immigrants who self-identify as healthy have high rates of undetected diabetes and prediabetes. Some 4.2% already have retinopathy, and require annual follow-up to monitor for progression. Vascular risk factors including hypertension and prediabetes were associated with retinopathy, and we would recommend screening at-risk individuals.

Impact of Vitamin B6 Intake on the Risk of Diabetic Retinopathy—Analysis from Multicenter Prospective Study of Japanese Patients with Type 2 Diabetes

CHIKA HÖRIKAWA, REI AIDA, SHIRO TANAKA, YUKIO YOSHIMURA, RYO KAWASAKI, TATSUNI MIYOTA, ATSUSHI AKARI, HIROHITO SONE, Niigata, Japan, Kaneto, Japan, Tokushima, Japan, Suita, Japan, Sagamihara, Japan, Tokyo, Japan

Vitamin B6 has been expected to prevent the progression of diabetic retinopathy. Previous studies reported that treatment with vitamin B6 protected against capillary dropout in a mouse model of diabetes and low serum vitamin B6 levels were associated with retinal vein occlusion in healthy individuals. However, data on this topic in patients with diabetes are sparse. As part of a nationwide cohort study we investigated the relationship between vitamin B6 intake and the incidence of diabetic retinopathy in Japanese patients with type 2 diabetes aged 40-70 years with HbA1c ≥6.5%. The present analysis was conducted among 2,005 Japanese patients with type 2 diabetes from outpatient clinics in 59 university and general hospitals in Japan. Analyzed were 1,516 responders to a baseline dietary survey assessed by the Food Frequency Questionnaire based on food groups. Primary outcome was the 6-year risk of a diabetic retinopathy event. Cox regression analyses estimated hazard ratios (HRs) for dietary intake adjusted for age, gender, body mass index, HbA1c, smoking, energy intake, and other confounders. Mean vitamin B6 intake in quartiles ranged from 0.9 to 2.0 mg/day and half of participants had vitamin B6 intake less than the recommended dietary allowance according to dietary reference intakes in Japan (males 1.4 mg/day; females 1.2 mg/day). Patients in higher quartiles included those with significantly high energy, vegetable, meat and fish intakes (p for trend < 0.01). We found that the mRNA levels of VEGF and RAGE in the HQAGE treated cells were increased. The additions of statins significantly high energy, vegetable, meat and fish intakes (p for trend < 0.01, < 0.01, < 0.01, and < 0.01, respectively). After adjusting for confounders, hazard ratios for diabetic retinopathy in the 2nd, 3rd, and 4th quartiles of vitamin B6 intake compared with the 1st quartile were 1.2 (95% confidence interval 0.8-1.7, p=0.36), 0.9 (0.6-1.3, p=0.51), and 0.5 (0.3-0.8), p=0.01, respectively. We clarified that the decreased incidence of diabetic retinopathy in Japanese patients with type 2 diabetes was associated with high vitamin B6 intake.

Supported By: Japan Society for the Promotion of Science

Compliance — Retinopathy

Supported By: Japan Society for the Promotion of Science

Acute and Chronic Complications

Supported By: Japan Society for the Promotion of Science

Moderated Poster Discussion

Supported By: Japan Society for the Promotion of Science

A157
Knowledge, Attitudes, and Practices Related to Diabetes Eye Complications among Diabetes Mellitus Patients at a Referral Hospital in Zimbabwe

MELISSA SITHOLE, ALICE MATIMBA, RICHMOND WOODWARD, Harare, Zimbabwe, New York, Italy

Information related to knowledge, attitudes, and practices of people with diabetes is especially important in resource-limited settings such as Zimbabwe, where medications to treat diabetes are costly and capacity to treat complications is limited, making observance of appropriate self-care practices that may delay or prevent complications vital to patient and public health. As a start to understanding the level of knowledge of diabetes eye complications, attitudes towards self-care practices, and utilization of available health care resources among diabetes patients, we conducted face-to-face interviews with 189 diabetes patients (133 female, 56 male, mean age 62.7 years) attending a referral hospital in Zimbabwe’s second largest city. A structured questionnaire was administered to each patient to document their knowledge, attitudes, and practices that had 13, 11, and 12 questions in each section respectively. Knowledge results revealed the total knowledge score of diabetes and associated eye complications is associated with patients’ self-report of seeing clearly or not, indicating patients not seeing all the time have a higher score than those patients self-reporting they do see clearly all the time, x²=24.5815, df=11, p=0.0105. Attitude results revealed 74% of participants viewed consulting a pharmacist as a very important health care step compared to 96% who viewed consulting a physician as a very important health care step. Results indicating patients with diabetes who see clearly have less knowledge about diabetes and related eye complications suggests that reinforcing self-care steps should be directed towards this group. At the same time, patient attitude results suggest this gap could be filled by emphasizing the role of pharmacists in fostering good diabetes self-care practices and providing education for individuals with diabetes, especially early in the course of disease before vision impairment may occur.

Male Type 2 Diabetic Patients Have Higher Diabetic Retinopathy Prevalence

SARA CHERCI, ALFONSO GIANGITA, PIERPAOLO CONTINI, DANILA PISTI, ROSANIELLA M. PILOSU, MARIA A. SPANU, MARIA A. FOIS, ALESSIO LAI, GISELLA MELONI, GIANCARLO TONDOLO, Olbia, Italy, Nuoro, Italy, Cagliari, Italy, Sassari, Italy, Isili, Italy, Lanusei, Italy

Diabetic retinopathy (DR) is one of the main causes of visual loss in individuals aged 20-64 years old. Some evidence indicates clear sex differences in diabetes complications, but studies focused on sex-gender differences in DR do not give clear data. The aim of this study was to investigate sex-gender differences in DR and prevalence in T2DM type 2 diabetic patients (T2DM). Methods: During 2015-2017 in seven diabetic outpatient clinics in Sardinia we examined under midriatic fundoscopy 19,951 (11,409 males, 8,542 females) T2DM with known diabetes duration more than 5 years. Patients were classified as having: a) No DR (NDR), b) Mild non-proliferative DR (NPNDR), c) Pre-proliferative and proliferative DR (RPDR), macular edema (ME). Each patient had full clinical and laboratory data available. In the same period in three diabetic outpatient clinics we performed also non midriatic retinography in other 1916 T2DM during the outpatient visit using a semi-automated digital fundus camera and each image was evaluated by an experienced diabetologist/oculist. Results: Diabetic retinopathy was more frequent under midriatic fundoscopy in males than females: (RDNP 15.9% vs. 14.3%, p<0.01 and RPDR 5.0% vs. 4.0%, p<0.001). Semi automated non midriatic retinography allowed to exclude DR in 68% of patients.

Conclusions: Our preliminary results indicate that: a) In this large sample of T2DM with known diabetes duration more than 5 years, DR is present in 24.1% of the subjects, with unit 3 having the highest prevalence (27.6%) and unit 6 the lowest (16.5%). b) P<0.0001 b) females have significantly less DR than males (p=0.0001), this effect is evident also excluding Unit 3 (p=0.0052). c) retinography may allow to exclude DR in almost 68% of outpatient T2DM patients avoiding the more expensive classical oculist assessment. Further analysis is under way in order to identify possible markers of sex-gender difference in DR.
Patients who underwent amputations, can be used as a stratified model in the propensity of stroke and mortality. The mortality in patients with DR was n=122) developed stroke (p<0.00001). Two or more fundus lesions increased years follow-up revealed high incidence of new amputations (n=610; NPDR (>15 years) corroborated with the high incidence of NPDR (n=421, 70%) and n=263 respectively; highest tertile of HbA1c (>15%) and duration of diabetes with amputations reported highest number of NPDR and PDR, n=561 and and hyperhomocysteinemia (p<0.00001). The age tertile of 40-60 years association for amputation of both limbs (n=640) (p<0.00001). Significant strong association with all types of amputations (p<0.00001), with highest of amputation. DR was observed in 56% patients [Non Proliferative DR screened for DR in year 2010, underwent Mini Mental State Examination amputations in 2500, T2DM patients (males 1295, females 1205) who were NAVNEET WADHWA, KIRAN SHAH, NATARAJAN SUNDARAM, ABHAY A. RAUT, SR., KARTHIK RAO, Seven‑Year Follow‑Up Mortality in Type 2 Diabetes Mellitus Patients with Amputations— Diabetes Retinopathy Grade as a Predictive Marker of Stroke and Mortality in Type 2 Diabetes Mellitus Patients with Amputations— A157 & 603-P Extreme Hyperglycemia Causes Vascular Hypoperfusion at Optic Nerve Head in Diabetic Patients (DM) TAKAKO MITSUMATSU, FUUMIKO YAGI, YUKI KONDO, AYAKO ANRAKU, SUMIE UKAHATA, KENTARU SAKAMOTO, GOUJI TUMITA, TERUO SHIBA, Tokyo, Japan Background: OCT angiography (OCTA) and laser speckle flowgraphy (LSFG) are novel and noninvasive imaging modalities which could evaluate fundus blood flow quantitatively. However, the role of OCTA and LSFG as diagnostic tools has not been widely investigated. Previous reports indicated that NO, reduced by hyperglycemia, exerts a key role for the autoregulation of retinal blood flow. We designed this study to evaluate the retinal blood flow by OCTA and LSFG in hyperglycemic DM. Method: 10 patients with extreme hyperglycemia at our outpatient clinic (FPG>250mg/dl, or casual PG>350mg/dl, age 58±5, 7 males, HbA1c 11.10±5%) and 32 healthy volunteers (age 48±2, 17 males) were included. Vascular density was calculated using OCTA. LSFG measured relative blood velocity (mean blur rate: MBR) in the optic nerve head (ONH). MBR-A (the mean of all area), MBR-V (the vessel mean) and MBR-T (the tissue mean) were analyzed. Result: OCTA revealed no difference between two groups in the vascular density at macula (47.37±1.14% for DM and 47.44±0.67% for NDM) and a tendency in the diabetic vascular density at ONH (40.14±3.56% for DM and 42.48±2.25% for NDM) without statistical significance. With LSFG, MBR-A and MBR-T did not exhibit significant differences, while MBR-V significantly decreased in DM compared to the healthy (42.85±2.05% for DM, 49.25±1.34% for NDM, p = 0.025). Discussion: Our results demonstrated that vascular hypoperfusion at ONH was associated with extreme hyperglycemia in DM with tendency to decrease in vascular density. It is generally supposed that the retinal blood flow decreases in DM and acute hyperglycemia. In DM actually presented physiological changes in the retina. Besides, there is a report that autoregulation of blood flow in the ONH is disrupted in diabetic retinas, as well as in healthy ones with uncoupled gap junctions. It is possible that the similar mechanisms are involved in ONH blood flow decrease observed in this study.

Diabetic Retinopathy Grade as a Predictive Marker of Stroke and Mortality in Type 2 Diabetes Mellitus Patients with Amputations— Seven-Year Follow-Up KIRAN SHAH, NATARAJAN SUNDARAM, ABHAY A. RAUT, SR., KARTHIK RAO, NAVNET WADHWA, Mumbai, India, Delhi, India We explored the association of grade of Diabetic Retinopathy (DR) with amputations in 2500, T2DM patients (males 1295, females 1205) who were screened for DR in year 2010, underwent Mini Mental State Examination (MMSE) for cognitive decline, and followed-up for 7 years, till 2017. Cohort was stratified into tertiles based on demographics, grade of DR and type of amputation. DR was observed in 56% patients [Non Proliferative DR (NPDR) n=962, 38%; Proliferative DR (PDR) n=438, 18%] demonstrating a strong association with all types of amputations (p<0.00001), with highest association of amputation of both limbs (n=604) (p<0.00001). Significant association was observed with comorbidities of hypertension, dyslipidemia and hyperhomocysteinemia (p<0.00001). The age tertile of 40-60 years with amputations reported highest number of NPDR and PDR, n=561 and n=263 respectively; highest tertile of HbA1c (>15%) and duration of diabetes (>15 years) corroborated with the high incidence of NPDR (n=421, 70%) and (n=449, 70%), respectively (p<0.00001). MMSE scores revealed a moderate to severe cognitive decline, NPDR (n=453) > PDR (n=231) (p<0.00001). Seven years follow-up revealed high incidence of new amputations (n=610; NPDR n=372, PDR n=238) (p<0.00001). 637 patients with DR (NPDR, n=515; PDR n=122) developed stroke (p<0.00001). Two or more fundus lesions increased the propensity of stroke and mortality. The mortality in patients with DR was 33.76% (n=844) of which 282 patients died due to stroke (p<0.00001). Overall, ischemic stroke was the leading cause of mortality in 83.82% patients, with lacunar stroke (n=340) as the commonest anatomical sub-type of stroke (p<0.00001). Patients with DR, especially with NPDR should be managed intensively to prevent fatal cerebrovascular events. Diagnosis of DR in patients who underwent amputations, can be used as a stratified model in association with comorbidities to predict stroke and the mortality.

Role of Xanthine Oxidoreductase from Mesenchymal Cells in Retinal Inflammation after Pericyte Breakdown AKIFUMI KUSHIYAMA, TAKAKO KIKUCHI, HIROKI YAMAZAKI, TAKESHI YAMA-MOTOYA, HIDEYUKI SAKODA, MIDORI FUJISHIRO, YUSUKE NAKATSU, AKIYOSHI UEMURA, TAKASHI SHIRAKURA, TOMOCHIHO ASANO, YASUHIKO IWAMOTO, Tokyo, Japan Hiroshima Japan, Miyasaki Japan, Nagoya Japan Glycemic control is important for diabetic retinopathy (DR), but not sufficient for the inhibition after proliferative DR (PDR). Uric acid in the vitreous is reportedly increased in patients with DR, especially in the PDR. Here, the involvement of xanthine oxidoreductase (XO), responsible for uric acid production, in worsening DR was examined in both mouse model and cultured angiogenesis model. First, retinal pericytes were abolished by anti-PDGFRβ antibody injection to C57/B16 neonatal mouse at P1. Pericyte drop-out from endothelial cells is reportedly early histological change in DR, and induces bleeding, abnormal angiogenesis, inflammation, and retinal detachment with rapid progression at P9-11. The expression of XO level in retina was increasing after pericyte breakdown, and was proportional to VEGF, and preceding the increase of TNFalpha. When 3.6mg/kg Febuxostat (Fbx), an XO inhibitor was injected at P7, widespread edema and retinal detachment/funnel-like deformation were dramatically improved by Fbx treatment at P11. ICAM-1+ cells surrounding edema and CD11b+ cells were reduced. Next, we performed a 3D culture sprouting assay using HUVEC spheroids in collagen gel co-cultured with human lung fibroblast (HLf) in fibrin gel. By Fbx treatment within the physiological concentration, the branch sprouting, cellular migration to the distal side and mitosis in branch stems were inhibited. ICAM-1 increase in HUVEC was observed with HLf co-culture but was suppressed by Fbx treatment. Finally, these effects of Fbx were not shown on HUVEC in planar culture. On the other hand, dissolution of fibrin by HLf was delayed directly due to Fbx. VEGF and PAI-1 expression from HLF and MMP-9 activity in medium were decreased by Fbx treatment. In summary, XO inhibition improved retinal inflammation and injury after pericyte loss. These results suggest the role of humoral inflammatory factors from mesenchymal cells surrounding retinal vessels in the hyperpermeable state such as DR.

Supported By: Japan Society for the Promotion of Science

Identification of Proliferative Diabetic Retinopathy to Asymptomatic Coronary Heart Disease in Chinese T2D Individuals—The IPAD Reach Study JIANBO ZHOU, JINKUI YANG, Beijing, China Aim: Substantial percentage of patients with T2D have asymptomatic Coronary Heart disease (CHD). To explore identification of PDR to asymptomatic CHD. We reported the baseline data from this IPAD reach group study, a China retrospective cohort study on clinical predictors of asymptomatic CHD in type 2 diabetes. Method: T2D individuals (211 non-DR (NDR) and 140 proliferative DR (PDR)) from a national diabetes center in China. The area under the receiver operating characteristic curve (AUC) were created. Discrimination and reclassification were used to assess the value of addition of PDR to the base model. Results: Investigation included 211 NDR and 140 PDR. With the model estimating risk of asymptomatic CHD based on UKFCS engine, the AUC analysis improved from 0.583 (95% CI, 0.51-0.66) to 0.639 (95% CI, 0.641-0.752) in the model without PDR and with PDR. The addition of PDR to a base model (8 traditional risk factors) to identify asymptomatic CHD increased the C statistic from 0.748 (95% CI, 0.681-0.811) to 0.762 (95% CI, 0.699-0.825, P=0.73). With the addition of PDR to the base model, there was a continuous net reclassification indexes (NRI) of 5.9% (95% CI, 1.4%-10.2%, p=0.017) for asymptomatic CHD. The absolute integrated discrimination index (IDI) was 0.004 (p=0.02), with a relative IDI of 10.4%.

Conclusions: The improvement in identification of asymptomatic CHD, compared with traditional risk factors, demonstrates that PDR could identify cardiovascular risk stratification in Chinese diabetic individuals. Follow-up of this cohort will provide reliable information on asymptomatic CHD risk.
Acute and Chronic Complications

606-P

608-P

Identification of Early Biochemical Changes in the Diabetic Retina Using an Unbiased Proteomics Approach
SARAH H. WEBER, YUANJUN ZHAO, ALISTAIR J. BARBER, CRISTINA HERNÁNDEZ, DILDA SIMÓ-SERVAT, THOMAS W. GARDNER, RAFAEL SIMÓ, JEFFREY M. SUNDSTROM, Henhey, PA, Barcelona, Spain; Ann Arbor, MI

Diabetic retinopathy (DR) remains a leading cause of blindness in developed countries. Current treatments target late stages of DR when vision has already been affected. The current study used an unbiased proteomic approach to gain a better understanding of early DR pathogenesis prior to clinically detectable microvascular lesions. During these early DR stages, neurodegeneration occurs and is marked by glial activation throughout the neuroretina. As glial activation increases, glial fibrillary acidic protein (GFAP) is upregulated and can be visualized histologically. Postmortem retinas from diabetic donors were divided according to the presence of abundant (n=5) or minimal (n=5) GFAP immunoreactivity and were compared to retinas from nondoniabetic donors with no known ocular pathologies (n=10). Retinal lysates from each group were pooled and run on an SDS-PAGE gel. Bands were analyzed sequentially by LC/MS using an Orbitrap Mass Spectrometer. A total of 2,190 proteins were identified across all groups. Pathway activation analysis was performed via Ingenuity Pathway Analysis. Pathways were subsequently grouped into broader functional categories based on the existing literature. Differential pathway analysis revealed significant differences between diabetic retinas with abundant vs. minimal GFAP immunoreactivity. Of particular interest are those pathways that function in both neuroprotective/neurodegenerative and angiogenic pathways, as they may represent a link between early and late diseases stages. Antioxidant/anti-inflammatory pathways, cell survival and apoptosis pathways, and autophagy also appear to play a role. Future studies will be required to confirm and extend these findings. Close analysis of these signaling changes may permit the development of preventive and interventional strategies for use in the early stages of DR, before overt microvascular damage or vision loss occurs.

Supported By: R01EY20582, R24DK082841, P1Y6/00541; A. Alfred Taubman Medical Research Institute

607-P

High-Fat Diet/Palmitate-Induced ER Stress Promotes Protein O-GlcNAcylation in Retina and Retinal Muller Cells
WEIWEI DAI, ALLYSON TÔRO, SADIE K. DIERSCHKE, MICHAEL D. DENNIS, Henhey, PA

The incidence of type 2 diabetes, the most common cause of diabetic retinopathy (DR), is rapidly on the rise due to the overconsumption of calorie rich diets. Using an animal model of diet-induced obesity/pre-type 2 diabetes, we evaluated the mechanistic responsible for increased O-GlcNAcylation of retinal proteins following consumption of a diet high in saturated fat (HFD). As dysregulated O-GlcNAcylation contributes to the development of DR. In the retina of mice fed a HFD for 4 weeks, increased O-GlcNAcylation was observed concomitant with markers of endoplasmic reticulum (ER) stress. Similarly, in TR-MUL retinal cells in culture, addition of the saturated fatty acid palmitate or the ceramic acid CerB to culture media increased the expression of protein O-GlcNAcylation and ER stress. One potential mechanism whereby ER stress increases O-GlcNAcylation is by upregulating flux through the hexosamine biosynthetic pathway (HBP) via increased expression of the rate-limiting enzyme glutamine-fructose-6-phosphate amidotransferase (GFAT). In the retina of mice fed a HFD and in TR-MUL cells exposed to CerB, mRNA and protein expression of GFAT2, but not GFAT1 were increased. Similarly, in TR-MUL cells treated with the ER stress inducer thapsigargin (Tg) increased O-GlcNAcylation was observed concomitant with an increase in GFAT2. Alternatively, ER stress inhibitor prevented the effect. GFAT2 knockdown via siRNA attenuated O-GlcNAcylation induced by either CerB or CerB.

The glial cell specific transcription factor OASIS (old astrocyte specifically-induced substance) plays a central role in coordinating the unfolded protein response. Unlike GFAT1, GFAT2 contains a putative binding site for OASIS. Induced substance) plays a central role in coordinating the unfolded protein response. Unlike GFAT1, GFAT2 contains a putative binding site for OASIS.

Supported By: American Diabetes Association/Pathway to Stop Diabetes (014-11N-04 to M.D.D.)

A160
Relationship between the Triglyceride Glucose Index and the Presence and Fibrosis of Nonalcoholic Fatty Liver Disease in Korean Adults

MIN KYUNG KIM, JIUNG HYE KIM, KAHUI PARK, JONG SANG, DAE BAE LEE, JI SUN NAM, SHINAE KANG, JONG SUK PARK, CHUL WOO AHN, YU SIK KIM, MIN KYUNG KIM, JUNG HYE KIM, KAHUI PARK, SANG BAE LEE, JI SUN NAM, SHINAE KIM.

Background: Recently, the triglyceride glucose (TyG) index has been considered a surrogate marker of insulin resistance. Insulin resistance is a well-known pathogenic factor in nonalcoholic fatty liver disease (NAFLD). However, few studies have investigated the relationship between the TyG index and liver fibrosis in subjects with NAFLD. Thus, we investigated the relationship between the TyG index and liver fibrosis in Korean adults.

Methods: In total, 5158 participants who underwent ultrasonography in a health promotion center were enrolled. Anthropometric profiles and multiple metabolic risk factors were measured. The TyG index was calculated as ln (fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2), and the insulin resistance index of homeostasis model assessment (HOMA-IR) was estimated. NAFLD was diagnosed by ultrasonography, and degree of liver fibrosis was assessed by NAFLD fibrosis score (NFS). Significant liver fibrosis was defined as NFS > -1.5.

Results: All subjects were stratified into four groups based on their TyG indices. Significant differences were observed in metabolic parameters among the groups, and the prevalence of NAFLD and liver fibrosis by NFS significantly increased with increasing TyG index. When classifying the severity of NAFLD into three groups, there was a significant correlation between the severity of NAFLD and the TyG index. In the logistic regression analysis after adjustment for multiple risk factors, the odds ratio for the prevalence of liver fibrosis, when comparing the highest and lowest quartiles of the TyG index was 1.92 (95% CI: 1.46-2.53; P for trend < 0.01); the odds ratio for the prevalence of liver fibrosis, when comparing the highest and lowest quartiles of HOMA-IR was 2.92 (95% CI: 1.12-2.40; P for trend < 0.01).

Conclusion: There is a significant association between the TyG index and liver fibrosis of NAFLD, but HOMA-IR was superior to TyG index for predicting liver fibrosis in NAFLD patients.

Relationship between Nitrated High-Density Lipoproteins and Vascular Function in African-American Diabetic Patients

AJIBOLA M. ADEDAVO, AYOBAMI ELULWOLE, FASIKAKA TDELA, ARYE KREMER, NICOLE MASTROGIOVANNI, CARL ROSENBERG, PAUL DREIZEN, JOHN LAROSA, LOUIS SALCIOCCI, MOHAMED BOUTJDIR, MARY ANN BANERJI, CLINTON BROWN, MORO SALIFU, JASON LAZAR, AHMED BAKILLAH, JI SUN NAM, NEW YORK.

Previous studies have shown that HDL isolated from human atherosclerotic lesions and the blood of patients with established coronary artery disease contains elevated levels of nitrated apolipoprotein A1 (NT-apoA1). The significance of NT-apoA1 in the pathogenesis of vascular diabetic complications is not well understood. We aimed to evaluate the relationship between plasma NT-apoA1 and vascular function in African-Americans diabetic patients. 125 patients with type 2 diabetes were enrolled over a 6 months period. Levels of plasma NT-apoA1 was quantified by enzyme-linked immunosorbent assay (ELISA). Microvascular function was assessed by vascular reactivity index (VRI). Large artery stiffness was assessed by carotid-femoral pulse wave velocity (PWV). Carotid intima-media thickness (CIMT) was assessed by B-mode ultrasound image analysis. Patients population was divided in two groups (well-controlled: HbA1c ≤ 7.0%, N=54; poorly-controlled: HbA1c >7.0%, N=71). Mean age 60+8 years; 64% female; 80% had hypertension; 80% had dyslipidemia and 15% had CKD. Mean HbA1c levels were 8.1±2.2% and duration of diabetes was 10.29±3.79 years. NT-apoA1 was negatively correlated with levels of apoA1 and VRI in well-controlled patients but not in poorly-controlled patients (r= -0.298, p=0.025 and r= -0.265, p=0.042; respectively). Multi-regression analysis revealed that NT-apoA1 was independently associated with VRI, but neither with PWV nor CIMT, after adjustment for independent variables such as age, gender, weight, hypertension, stroke, smoking, duration of diabetes, dyslipidemia, total cholesterol, HDLc, triglycerides, and LDLc (β= -0.001, p= 0.925; β= 0.325 for the model). NT-apoA1, independently of other clinical variables, can predict microvascular dysfunction particularly in well-controlled diabetic patients. NT-apoA1 could be used as marker to identify diabetic patients at risk of developing early vascular complications.

Lipoprotein(a) Levels Are Twice as High in Left ‑Handed T2DM Patients

JIANNIN RAN, XIMING PAN, RUIYI ZHANG, PING ZHUL, RONGSHAO TAN, YAN LIU, Guangzhou, China

Background: What and how the adipose-derived ApoE regulates biological features and lipid metabolism in the diabetic adipose tissue remain little known.

Methods: ApoE−/- and wild type mice were randomly divided into 4 groups: ApoE−/- group (EKO); streptozotocin (STZ)-induced diabetic apoE−/- group (EKODM); wild type group (WT); and STZ-induced diabetic wild type group (WTDM). Epididymal white adipose tissue isolated from each group (EKO and WTDM) were minced into small pieces and incubated at 37°C in Eagle’s medium with 10% fetal bovine serum for 2 hours. Then, the adipocytes treated with insulin and supplemented with low glucose (6.7 mM) and high glucose (25 mM) for 24 hours. Next, lipid accumulation was measured by Nile Red staining, and the expression of LPL, and LCAT was measured by real-time PCR.

Results: All subjects were stratified into four groups based on their TyG indices. Significant differences were observed in metabolic parameters among the groups, and the prevalence of NAFLD and liver fibrosis by NFS significantly increased with increasing TyG index. When classifying the severity of NAFLD into three groups, there was a significant correlation between the severity of NAFLD and the TyG index. In the logistic regression analysis after adjustment for multiple risk factors, the odds ratio for the prevalence of liver fibrosis, when comparing the highest and lowest quartiles of the TyG index was 1.92 (95% CI: 1.46-2.53; P for trend < 0.01); the odds ratio for the prevalence of liver fibrosis, when comparing the highest and lowest quartiles of HOMA-IR was 2.92 (95% CI: 1.12-2.40; P for trend < 0.01).

Conclusion: There is a significant association between the TyG index and liver fibrosis of NAFLD, but HOMA-IR was superior to TyG index for predicting liver fibrosis in NAFLD patients.
Results: Non-RHs had a stronger family history of early-onset CVD, were more insulin-sensitive, and were less often treated with insulin. RHs and non-RHs did not differ as regards use and intensity of statins, routine lipids, and lipoproteins are unaffected by motor laterality. Elevated Lp(a) in left-handers also underlies higher LDL-C before statins, yet did not differ between groups, suggesting better response/compliance to 37.0 vs. 18.7 nmol/L in RHs; p 0.0018), resulting in 32% of non-RHs having size. In contrast, Lp(a) levels were significantly higher in non-RHs (median 24.20% 45.65% 78.72%<0.0001<0.0001<0.0001). Background: The plasma concentration of arachidonic acid, one of the omega-6 long-chain polyunsaturated fatty acids (LCPUFAs), was increased by the treatment of statin in several clinical studies indicating that statin affects the endogenous synthesis of LCPUFAs, which is regulated by the action of the fatty acid desaturases (FADs) and elongation of very long-chain fatty acids (ELOVLs).

Aims: We investigated the roles of the intrinsic mevalonate cascade and rho-dependent pathway in the statin-induced regulation of these desaturases and elongases using human hepatocellular carcinoma cell line Hepg2 cells.

Methods: Cell viability was assessed by measuring mitochondrial activity of WST-8, and the activity of caspase-3 and -7 (caspase-3/7) was measured. Gene expression was analyzed by quantitative real-time PCR. Protein expressions were detected by Western blot analysis.

Results: Although atorvastatin decreased the cell viability with increasing activity of caspase-3/7 in a dose-dependent manner, both mRNA and protein expression of FADS2 was stimulated by atorvastatin at lower dose of 12.5 and 25 μM, where mRNA expression of FADS1 and Elov5 also increased. Both mevalonate and geranylgeranyl-pyrophosphate (GGPP), not cholesterol, fully restored the atorvastatin-induced inhibition of cell viability, and the atorvastatin-induced upregulation of mRNA and protein of FADS2. The Rho-associated protein kinase (ROCK) inhibitor Y-27632 inhibits the restoration of mevalonate and GGPP. Both EPA and DHA, but not AA, significantly suppressed the atorvastatin-induced upregulation of gene expression of FADS1, FADS2 and Elov5.

Conclusions: These data demonstrated that statin may affect the endogenous synthesis of LCPUFAs by the regulation of these desaturases and elongases through GGPP-dependent rho kinase pathway in Hepg2 cells.

**Table 1.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal (n=667)</th>
<th>PD (n=442)</th>
<th>DM (n=108)</th>
<th>P-Among Groups</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>213 (194-249)</td>
<td>213 (194-249)</td>
<td>208 (182-245)</td>
<td>&lt;0.0001</td>
<td>0.02</td>
</tr>
<tr>
<td>HDL</td>
<td>49 (43-60)</td>
<td>40 (34-48)</td>
<td>38 (34-48)</td>
<td>&lt;0.0001</td>
<td>0.16</td>
</tr>
<tr>
<td>Non-HDL-cholesterol</td>
<td>167 (135-196)</td>
<td>176 (125-186)</td>
<td>172 (139-183)</td>
<td>&lt;0.0001</td>
<td>0.02</td>
</tr>
<tr>
<td>Hepatic steatosis</td>
<td>24.20%</td>
<td>45.65%</td>
<td>78.72%</td>
<td>&lt;0.0001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Association between Metabolic Syndrome Components and Indices of Liver Steatosis and Stiffness by Transient Elastography in Patients with Type 2 Diabetes and Imaging-Confirmed Nonalcoholic Fatty Liver Disease**

ZHIMIN HUANG, CHI HO LEE, HO YI FONG, KAREN S. LAM, Guangzhou, China, Hong Kong, China

**Background and Aims:** The index of liver steatosis, controlled attenuation parameter (CAP), is a relatively new introduction to transient elastography equipment for assessing liver fibrosis, in terms of liver stiffness measurement (LSM). The relationship between CAP and/or LSM and metabolic syndrome components in diabetic patients with nonalcoholic fatty liver disease (NAFLD) was unclear, and was addressed in this study.

**Methods:** A total of 224 patients with type 2 diabetes and NAFLD confirmed by ultrasonography were recruited. Anthropometric and serum biochemical parameters were collected. CAP and LSM were measured using transient elastography. The association between metabolic syndrome components and values of CAP and LSM was analyzed.

**Results:** The mean age of the patients was 57.9±10.2 years, their BMI was 28.2±5.9 kg/m², and the duration of diabetes was 16.8±8.3 years. Eighty-eight percent of the patients had hypertension, and 79.5% were on lipid-lowering drugs. The mean CAP was 309.3±57.9 dB/m, and median LSM was 7.9 (5.7, 10.4) kPa. There were significant trends in BMI, waist circumference, waist to hip ratio, white blood cell count, HbA1c, FPG, triglyceride, ALT, AST and LSM with escalating CAP tertiles, whereas age, HDL-c, AST/ALT ratio and plasma adiponectin decreased concomitantly (all p<0.05). There was a large number of metabolic syndrome components clustering in the third as compared to the first tertile of CAP (p=0.027) and LSM (p=0.050). On the other hand, with an increasing number of metabolic syndrome components, the value of CAP (p=0.001) and LSM (p=0.025) increased accordingly.

**Conclusion:** CAP and LSM measured by transient elastography had a strong correlation with the clustering of metabolic syndrome components in NAFLD, even in patients with long-standing type 2 diabetes.
levels had a disproportionate benefit on endothelial NO and ONOO− release using immunochemical approaches. Results showed that reductions in LDL reduced from 150 to 70 mg/dL with regard to the NO-to-ONOO− release ratio. Also correlated with increased eNOS dimer formation by 819%. By contrast, 0.40; p<0.0001), a comprehensive indicator of EC function. These changes during Hyperglycemia during Hyperglycemia during Hyperglycemia.

Supported By: Amgen Inc.

Increased Angiopoietin Like Proteins 4 (ANGPTL4) Is Associated with Higher Concentration of LDL-Triglycerides in Type 2 Diabetes

HIRIE M. NAGAIKE, TOSHIYUKI HAYASHI, NORIKO NAKANISHI, MAKOTO OHARA, TAKESHI YAMAKOTI, TOMOTASU FUKUI, TSUTOMU HIRANO, Tokyo, Japan

Background/Aims: Diabetic dyslipidemia is typically characterized by an increase in plasma triglycerides (TG), a concomitant increase in small dense (sd) low density lipoprotein (LDL) and atherogenic LDL-TG. Angiopoietin like protein 4 (ANGPTL4) is well established regulators of plasma TG level through regulating the activity of lipoprotein lipase. Plasma level and association between ANGPTL4 and sdLDL-C or LDL-TG is not well established in human subjects. We aimed to examine the level of ANGPTL4 and investigate the association between ANGPTL4 with sdLDL-C and LDL-TG in type 2 diabetes (T2D).

Methods: 260 (M176F 74) Japanese diabetic patients and 9 of healthy controls (Controls) were enrolled in this study. SDLDL-C and LDL-TG were measured by homogeneous assays. ANGPTL3 and ANGPTL4 protein levels were measured by ELISA.

Results: As compared with Controls, plasma ANGPTL3, ANGPTL4, sdLDL-C and LDL-TG levels were increased in T2D. ANGPTL3 was not collated with sdLDL-C or LDL-TG. ANGPTL4 was positively correlated with HbA1c (r=0.15, p=0.019), TG (r=0.15, p=0.018) and LDL-TG (r=0.17, p=0.008), whereas ANGPTL4 was not collated with sdLDL-C. Furthermore, ANGPTL4 was also significantly associated with LDL-TG/LDL-C-ratio (r=0.15, p=0.022) and LDL-TG/apoB ratio (r=0.18, p=0.036).

Conclusions: The ANGPTL4 level was increased in T2D and associated with atherogenic higher LDL-TG levels. ANGPTL4 may play a role in modulating lipid metabolism in LDL particles.

Supported By: Denka Seiken Co., Ltd

Progressive Improvement in Endothelial Nitric Oxide Release due to Synthase Dimer Formation with LDL Reductions below 70 mg/dL during Hyperglycemia

R. PRESTON MASON, HAZEM E. DAWOD, SR., SAMUEL SHERBATT, TADEUSZ MALINSKI, Beverly, MA, Athens, OH

In diabetes, endothelial cell (EC) dysfunction is characterized by reduced nitric oxide (NO) release and increased nitrooxidative stress due to NO synthase (eNOS) dimer uncoupling. Reductions in LDL improve EC function but the effect is not well understood at levels below the target of 70 mg/dL. We measured NO and peroxynitrite (ONOO−) release as well as eNOS dimer formation in ECs under hyperglycemic conditions following progressive reductions of LDL in vitro. Human umbilical vein endothelial cells (HUVECs) were incubated with LDL at concentrations ranging from 150 to <10 mg/dL with high glucose (250 mg/dL). Cells were stimulated with calcium ionophore, and assayed for NO and ONOO− release using porphyrinic sensors. eNOS dimer levels were measured using immunochemical approaches. Results showed that reductions in LDL levels had a disproportionate benefit on endothelial NO and ONOO− release below 70 mg/dL. A reduction in LDL levels from 70 to <10 mg/dL produced a 181% increase in NO release (133 ± 18 to 458 ± 34 nM, p<0.0001) and 116% decrease in NOO− release (393 ± 27 to 182 ± 2.3 nM; p<0.0001), corresponding to a 513% increase in the NO-to-NOO− release ratio (0.42 ± 0.04 to 2.56 ± 0.40; p<0.0001), a comprehensive indicator of EC function. These changes also correlated with increased eNOS dimer formation by 819%. By contrast, only a modest 27% change in EC function was observed as LDL levels were reduced from 150 to 70 mg/dL with regard to the NO-to-ONOO− release ratio. In the absence of hyperglycemia, the benefits of LDL lowering on EC function and eNOS dimerization were also very evident, but to a lesser extent. Thus, progressive improvements in endothelial NO bioavailability and eNOS dimer formation were observed at LDL levels below 70 mg/dL to <10 mg/dL. These results support the hypothesis that LDL reductions to very low levels may be effective in reversing EC dysfunction for the diabetic patient.

Supported By: Amgen Inc.

Increased Angiopoietin Like Proteins 4 (ANGPTL4) Is Associated with Higher Concentration of LDL-Triglycerides in Type 2 Diabetes

Background/Aims: Diabetic dyslipidemia is typically characterized by an increase in plasma triglycerides (TG), a concomitant increase in small dense (sd) low density lipoprotein (LDL) and atherogenic LDL-TG. Angiopoietin like protein 4 (ANGPTL4) is well established regulators of plasma TG level through regulating the activity of lipoprotein lipase. Plasma level and association between ANGPTL4 and sdLDL-C or LDL-TG is not well established in human subjects. We aimed to examine the level of ANGPTL4 and investigate the association between ANGPTL4 with sdLDL-C and LDL-TG in type 2 diabetes (T2D).

Methods: 260 (M176F 74) Japanese diabetic patients and 9 of healthy controls (Controls) were enrolled in this study. SDLDL-C and LDL-TG were measured by homogeneous assays. ANGPTL3 and ANGPTL4 protein levels were measured by ELISA.

Results: As compared with Controls, plasma ANGPTL3, ANGPTL4, sdLDL-C and LDL-TG levels were increased in T2D. ANGPTL3 was not collated with sdLDL-C or LDL-TG. ANGPTL4 was positively correlated with HbA1c (r=0.15, p=0.019), TG (r=0.15, p=0.018) and LDL-TG (r=0.17, p=0.008), whereas ANGPTL4 was not collated with sdLDL-C. Furthermore, ANGPTL4 was also significantly associated with LDL-TG/LDL-C-ratio (r=0.15, p=0.022) and LDL-TG/apoB ratio (r=0.18, p=0.036).

Conclusions: The ANGPTL4 level was increased in T2D and associated with atherogenic higher LDL-TG levels. ANGPTL4 may play a role in modulating lipid metabolism in LDL particles.

Supported By: Denka Seiken Co., Ltd

A Neural Signature of Metabolic Syndrome—Preliminary Results

EITHAN KOTKOWSKI, CRYSTAL FRANKLIN, PETER T. FOX, San Antonio, TX

As of 2012, metabolic syndrome (MetS) has been estimated to impact 34.7% of the U.S. population (Aguilar, 2015). Meeting the criteria for MetS increases one’s risk for developing cardiovascular disease and type 2 diabetes mellitus (T2DM). However, only recently have researchers begun to probe its effects on brain structure and function. Recent studies have shown that in humans, increased levels of obesity and hyperglycemia are correlated with decreased executive function, processing speed, memory, as well as higher incidences of depression, among others (Yates, 2012). Evidence also suggests that effects of MetS and neurocognitive dysfunction are bidirectional and complex, with genetic, environmental, and behavioral causes playing an important role (Bassiels, 2014). In our study, we use voxel-based morphometry (VBM), a well-established structural MRI imaging analysis, to investigate regional gray matter atrophy differences between age- and sex-matched healthy controls (n=108) and individuals meeting the International Diabetes Federation criteria for MetS (n=108) from a homogenous Mexican-American cohort. We find that, indeed, there is a significant difference in gray matter density between individuals meeting the criteria for MetS and their age- and sex-matched healthy controls with statistically significant involvement in the following brain regions: bilateral caudate nuclei, orbitofrontal cortex, right parahippocampus/amygdala, right posterior insula, and posterior cerebellum. Additionally, when regressing out key components of MetS such as waist circumference and obesity, we find diverging gray matter atrophy patterns suggesting differential involvement of MetS components on gray matter structure.

Supported By: National Institutes of Health (3R01MH020457-11S1)
**Acute and Chronic Complications POSTERS**

Triglycerides vs. ApoC-III

<table>
<thead>
<tr>
<th>Parameters</th>
<th>R²</th>
<th>p-value</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL vs. ApoC-III</td>
<td>0.83</td>
<td>&lt;0.001</td>
<td>28</td>
</tr>
<tr>
<td>HDL vs. ApoC-III</td>
<td>0.76</td>
<td>0.267</td>
<td>19</td>
</tr>
<tr>
<td>Insulin vs. ApoC-III</td>
<td>0.74</td>
<td>0.195</td>
<td>19</td>
</tr>
</tbody>
</table>

**Parameters**

- LDL: low-density lipoprotein
- HDL: high-density lipoprotein
- Insulin: hormone that regulates blood sugar levels

**Results:**

The study observed a significant relationship between triglycerides and ApoC-III, indicating that circulating ApoC-III levels also correlate with insulin resistance, and HbA1c. These results reiterate the tight relationship observed using linear regression analyses between circulating ApoC-III levels and investigated parameters. These results reiterate the tight relationship between triglyceride levels and ApoC-III levels, and further demonstrate that circulating ApoC-III levels also correlate with insulin resistance, and HbA1c as well as important left ventricle morphometric parameters. It is plausible to hypothesize that a strategy to lower apoC-III levels may have additional benefits beyond lowering triglyceride levels.

**Conclusion:**

The relationship between triglycerides and ApoC-III levels observed in this study highlights the potential importance of targeting ApoC-III as a therapeutic strategy to improve metabolic parameters and reduce cardiovascular risk.

---

**624-P**

**Effects of Gly-LDL on LRPS/DKK1 Pathway in MC3T3-E1 Osteoblasts**

TAO LEI, LIN CHEN, BINGYU ZHANG, WENJUN TANG, Shanghai, China

**Background:**

The aim of this study was to investigate the effect of glycated low density lipoprotein (Gly-LDL) on the proliferation, differentiation and expression of low-density lipoprotein receptor-related protein 5 (LRPS), dickkopf 1 (DKK1) in mouse MC3T3-E1 cells.

**Methods:**

The MC3T3-E1 cells were cultured with native LDL (n-LDL) without chemical, and various levels of Gly-LDL was cultured respectively with 5mg/ml/L, 20mg/ml/L, 100mg/ml/L (D-glucose for 4 weeks) for 48h. The proliferation of MC3T3-E1 cell was measured by CCK8, the osteocalcin level in the medium was determined by ELISA, the mRNA expression of LRPS, β-catenin and DKK1 was analysed by real-time PCR and proteins in Wnt signaling pathway by western blot.

**Results:**

After cells incubation with group A of Gly-LDL, the inhibition of MC3T3-E1 cells was significantly promoted than that of n-LDL control group (P<0.01), the higher Gly-LDL level the more inhibited. The effects of Gly-LDL on the proliferation of MC3T3-E1 was dose-dependent under certain conditions. The levels of Osteocalcin in cells cultured with Gly-LDL were significantly inhibited compared with the control group. The mRNA expression of DKK1 was significantly up-regulated while the mRNA expression of β-catenin and LRPS were down-regulated (P<0.01) in MC3T3-E1 cells, which cultured with group A Gly-LDL. According to the results of western blot, it also showed that, compared with n-LDL group, the effect of Gly-LDL on osteoblasts was down-regulated the LRPS and β-catenin while up-regulated the DKK1.

**Conclusions:**

The Wnt signaling pathway being involved might be the possible mechanism of Gly-LDL effect on the proliferation and differentiation in MC3T3-E1 cells.

---

**625-P**

**Effect of Ezetimibe Add-On Therapy on Non-HDL-C in Type 2 Diabetes Subjects—A Post-Hoc Analysis of RESEARCH Study**

KENTARO SAKAMOTO, MITSUNOBU KAWAMURA, MATOKI TAGAMI, AKIRA TANAKA, YASUCHIHI MURU, TSUTOMU HIROKI, TERUO SHIBA, RESEARCH STUDY GROUP, Tokyo, Japan

**Background:**

In RESEARCH study, we demonstrated the superiority of ezetimibe add-on therapy over statin-doubling in T2DM. Non-HDL-C is attracting attention as an index including TG rich lipoproteins reflecting insulin resistance in diabetics.

**Methods:**

109 T2DM adults with LDL-C >120 mg/dl (n=100 mg/dl in secondary preventive) despite statin treatment were randomly assigned to statin doubling group (S) or adding ezetimibe (E) for 12 weeks. As a post-hoc analysis, non-HDL-C change and TG rich lipoproteins were analyzed.

**Results:**

The rate of non-HDL-C reduction was significantly greater in E (20.9%) than in S (8.3%). Assuming the non-HDL-C target as ≤150 mg/dl (≤130 mg/dl for secondary preventive) despite statin treatment were randomly assigned to statin doubling group (S) or adding ezetimibe (E) for 12 weeks. As a post-hoc analysis, non-HDL-C change and TG rich lipoproteins were analyzed.

**Conclusion:**

Ezetimibe combination therapy effectively reduced non-HDL-C reflecting TG rich lipoproteins, compared with statin-doubling therapy.

**Supported By:** Japan Vascular Disease Research Foundation
Effects of High-Intensity Statins on Glucose Homeostasis in Patients with Type 2 Diabetes

NUITAKORN THONGTANG, SUTIN SRIUSSADAPORN, NATHAKAN TANGTIKAESM, Bangkok, Thailand

Statin use has been reported to increase the risk of new onset diabetes, and potentially worsen glycemic control in patients with type 2 diabetes (T2D). The risk of new onset diabetes from statin is higher with increased dose of statin administration. This study was aimed to evaluate the effects of high-intensity statins as compared to the lower intensity statins on glu- cose homeostasis and glycemic control in patients with T2D. T2D who were taking simvastatin up to 20 mg/day (N=100) were randomized to continue using the same dosage of simvastatin (low- to moderate-intensity statin group; LS) for 12 weeks or change to atorvastatin 40 mg/day for 6 weeks and if tolerable increased to atorvastatin 80 mg/day for 6 weeks (high- intensity statin group; HS). Fasting plasma glucose (FPG), HbA1c, fasting plasma insulin, HOMA-IR and HOMA-B were measured at baseline, 6 weeks, and 12 weeks. Oral hypoglycemic agents were unchanged throughout the study period and patients who were on human insulin were excluded from the analysis. Ninety-eight patients completed the study (73% female), mean age 59.9±6 years, mean BMI 27.3±4.5 kg/m², mean duration of diabetes was 10±(48-180) months. Mean baseline FPG and HbA1c were 130±45.3 mg/dl and 6.9±0.9%, respectively. Median baseline insulin level, HOMA-IR, and HOMA-B were 10.6 (7.5-17.1) mU/l, 3.3 (2.2-5.5), and 65.5 (37.7-13.8), respectively. There was no significant difference in baseline characteristic and baseline glucose homeostasis parameters between the LS (n=49) and HS group (n=51). There was a slight increase in HbA1c in the HS group as compared to the LS group at 6 weeks (+0.1% vs. 0%, p<0.05), and 12 weeks (+0.1% vs. -0.1%, p=0.13) respectively. However, there were no significant changes in FPG, fasting plasma insulin, HOMA-IR and HOMA-B between the LS and HS group.

In conclusion, there was no significant deterioration in glucose homeosta- sis with high-intensity statins as compared to low dose statins in patients with T2D.

Supported By: Pfizer Inc.

Enhancement of Insulin Sensitivity Contributes to Polychlorinated Biphenyl-126-Induced Hepatic Steatosis and Injury

XIN WANG, SRI, Xian, China

Background: In the last decades, the prevalence of diabetes and related metabolic disorders has a dramatic increase. The global prevalence of diabetes and its related disorders is closely associated with the exposure to polychlorinated biphenyls (PCBs).

Aim: To investigate the the effect of PCB-126 on glucose/lipid metabolism and hepatic steatosis and to elucidate the molecular mechanisms.

Methods: C57BL/6J mice were orally administered with PCB-126 (1.5 mg/kg) twice in a week with or without the injection of GDC-0941 (1 mg/kg) before the administration of PCB-126. The experimental period was two weeks.

Results: PCB-126 significantly decreased fasting blood glucose level, reduced glucose levels in the glucose and insulin tolerance tests, indicat- ing that PCB-126 treatment increased insulin sensitivity in mice. In addition, PCB-126 exposure resulted in a significant increase in hepatic lipid content, as reflected by biochemical determination. Oil Red O staining and Bodipy staining. Using transmission electron microscopy, we observed that PCB-126 increased the number and size of lipid droplets in liver tissues. We showed that injection of GDC-0941, an inhibitor of insulin signaling, slightly inhibited the effect of PCB-126 on glucose levels and glucose and insulin tolerance.

Although GDC-0941 did not significantly affect the content of triglyceride in liver of PCB-126-treated mice, the size of hepatic lipid droplet was signifi- cantly reduced by GDC-0941, as evidenced by Bodipy staining and observation under transmission electron microscope. Moreover, PCB-126-induced expres- sion of any hydrocarbon receptor and lipogenesis-related regulators, such as sterol regulatory element-binding protein 1, was inhibited by GDC-0941.

Conclusion: The data suggest that enhancement of insulin sensitivity con- tributes to PCB-126-induced hepatic steatosis and injury.

Supported By: National Natural Science Foundation of China (21677178)

Ophthalmologic Findings in Congenital Generalized Lipodystrophy—A Possible Marker of Metabolic Disorders


Background and Aims: Metabolic disorders can present ophthalmologic changes. Congenital Generalized Lipodystrophy (CGL) is characterized by severe metabolic manifestations such as insulin resistance, diabetes and hypertriglyceridemia, but there are few published reports about ophthalmologic findings in this condition. The purpose of this study is to describe ocular manifestations of CGL.

Methods: A total of 19 patients with CGL were included. The ages ranged from 2 months to 31 years. The entire ocular examination was performed.

Results: All subjects had dyslipidemia: 15/15 (100%) hypertriglyceridemia; 15/15 (100%) low HDL-c; 4/15 (26.7%) and high levels of LDL-c. Diabetes was presented in 7/15 (46.7%) cases. Symptoms of surface eye disease (blurred vision, pruritus, hyperemia or dry eye sensation) were presented in 9/15 (60%) patients and 8/15 (53%) had refractive errors: 5/8 (62.5%) astigma- sis, 2/8 (25%) myopia and 1/8 (13%) myopia and astigmatism. In the slit lamp, 12/15 (80%) presented anterior blepharitis (seborrheic or melibotis), 13/15 (87%) decrease in the break up time of the tear (less than 8 seconds) and 5/15 (33.3%) keratitis. In the funduscopy, 2/15 (13.3%) presented retinopathy (one with nonproliferative diabetic retinopathy and another pre- sented proliferative diabetic retinopathy).

Conclusion: These findings demonstrate high frequency of blepharitis and its complications in patients with CGL, even in young subjects without diabetes. These data allow us to speculate that the presence of abnormalities in the anterior segment of the eye may be a marker of metabolic disorders as dyslipidemia and insulin resistance.

Supported By: Warsaw Medical University

Foot Care—Lower Extremities

Acute and Chronic Complications

Posters: 628-P to 635-P, see page 25.

Inflammation in Congenital Generalized Lipodystrophy is Mediated by Aryl Hydrocarbon Receptor and Lipogenesis-Related Regulators

TIA BAKI, BEATA MROZIKIEWICZ-RAKOWSKA, MATEUSZ MIECZKOWSKI, TOMASZ TIKASEM, NUNTAKORN THONGTANG, SUTIN SRIUSSADAPORN, NATTHAKAN TANGKITWONG, Xi’an, China

Aim: To investigate the effect of PCB-126 on glucose/lipid metabolism and hepatic steatosis and to elucidate the molecular mechanisms.

Methods: C57BL/6J mice were orally administered with PCB-126 (1.5 mg/kg) twice in a week with or without the injection of GDC-0941 (1 mg/kg) before the administration of PCB-126. The experimental period was two weeks.

Results: PCB-126 significantly decreased fasting blood glucose level, reduced glucose levels in the glucose and insulin tolerance tests, indicat- ing that PCB-126 treatment increased insulin sensitivity in mice. In addition, PCB-126 exposure resulted in a significant increase in hepatic lipid content, as reflected by biochemical determination. Oil Red O staining and Bodipy staining. Using transmission electron microscopy, we observed that PCB-126 increased the number and size of lipid droplets in liver tissues. We showed that injection of GDC-0941, an inhibitor of insulin signaling, slightly inhibited the effect of PCB-126 on glucose levels and glucose and insulin tolerance.

Although GDC-0941 did not significantly affect the content of triglyceride in liver of PCB-126-treated mice, the size of hepatic lipid droplet was signifi- cantly reduced by GDC-0941, as evidenced by Bodipy staining and observation under transmission electron microscope. Moreover, PCB-126-induced expres- sion of any hydrocarbon receptor and lipogenesis-related regulators, such as sterol regulatory element-binding protein 1, was inhibited by GDC-0941.

Conclusion: The data suggest that enhancement of insulin sensitivity con- tributes to PCB-126-induced hepatic steatosis and injury.

Supported By: National Natural Science Foundation of China (21677178)
Depression and Anxiety Associated with Complications after Foot and Ankle Surgery in Diabetic Patients—Comparison with a Non-diabetic Population

KRISTIN KIRBY, KIMBERLEE HOBIZAL, RENEE SHEPHERD, TRESA WIZE, BEAVER, PA

The purpose of this study is to evaluate and compare the complication rates in diabetic patients with a history of depression and anxiety than those without diabetes following foot and ankle surgery. Diabetes and a diagnosis of depression have shown to increase post-surgical complication rates in other specialties including cardiothoracic surgery and plastic surgery. 106 patients who were surgically treated by one surgeon at one hospital with foot and ankle conditions were retrospectively reviewed, identifying 28 patients with diabetes, 14 diabetic patients with depression, 1 with anxiety and 2 with both depression and anxiety. In comparison, there were 78 patients without diabetes identified and of those 78 subjects, 22 had depression, 3 with anxiety and 9 with both depression and anxiety. The primary outcomes evaluated were the rates of post-surgical complications and glycemic control. Diabetes, depression and anxiety was confirmed by diagnosis history and treatment. Most common complications included superficial soft tissue infection (SSI) and incisional dehiscence/delayed healing. Diabetic patients with a history of depression and anxiety had a 1.8 times higher likelihood to develop a post-surgical complication. Patients with diabetes with a history of a psychological disorder showed a complication rate of 28%. The complication rate associated with a psychological disorder without diabetes was 15%. In the 106 patients, a psychological disorder was noted in 80% of the diabetic patient cases and for the group without diabetes was noted to be 43.5%. The mean HgbA1c of the 28 diabetic patients without complications included a mean of 6.5.

The presence of depression and anxiety in a diabetic patient negatively impacts the outcomes of patients undergoing foot and ankle surgery resulting in a higher likelihood of post-surgical complications in compared to those without diabetes.

3D Microstructural Fiber Tracking of the Human Calf Muscles in Individuals With and Without Type 2 Diabetes during Rest and Exercise

MASOUD EDALATI, CHRISTOPHER J. SORENSEN, MARY HASTINGS, MOHAMED A. ZAYED, MICHAEL J. MUELLER, JIE ZHENG, ST. LOUIS, MO

Aim: This work explores underlying microstructural fiber differences in the calf muscles of individuals with and without type 2 diabetes mellitus (DM) at rest and during an isometric exercise.

Methods: Twenty-one subjects were examined in a 3T MRI scanner. Two groups were tested: 8 participants without DM (WDM) and 13 participants with DM. We used a custom-made MRI compatible ergometer that consisted of a brake-like pedal with an adjustable pressure gauge. Diffusion tensor imaging was performed on calf at rest and during a plantarflexion exercise. Regions of interests (ROI) were manually drawn on medial and lateral gastrocnemius (MG and LG), as well as on soleus (SOL).

Results: In the MG, the fiber length changes (%) were -29.07±6.71 for the WDM, and -52.53±15.06 for the DM group (p<.001). Exercise fiber density (P=<.01) and angle (P=<.05) changes were also significantly different between groups. The DM resulted in more fiber disarrays with loss of fiber during exercise (Figure).

Conclusions: While more changes in the fiber indices were observed in the DM during exercise, significant difference was shown in the MG muscle. These changes may reflect diabetic damage by altering muscle microstructure.

Renal Function as a Predictor of Reamputation after Initial Transmetatarsal Amputation in the Perioperative Period—An ACS-NSQIP Study

JUNHOO AHN, KATHERINE M. RASPOVIC, TRAPPER LALLI, GEORGE T. LIU, MICHAEL D. VANPELT, DANE WUKICH III, DALLAS, TX

Previous reports correlating renal function and reamputation after transmetatarsal amputation (TMA) have been mixed. This study aims to evaluate renal function as a factor for reamputation after initial TMA during the perioperative period in a large population database.

Patients who underwent TMA were identified in the American College of Surgeons-National Surgical Quality Improvement Program® database. Reamputation was defined as unplanned TMA or higher-level amputation in the 30-day perioperative period. Glomerular filtration rate (eGFR) was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Of 1,775, the rate of reamputation was 6.5%. Reamputation was correlated with higher white blood cell counts (p<.00001), greater serum creatinine (p=.021), higher blood urea nitrogen (p=.021), type of glycemic control (p=.021), stage of CKD (p=.003), and dialysis (p=.001). CKD stage was directly associated with higher white blood cell counts (p<.00001), greater serum creatinine (p=.021), higher blood urea nitrogen (p=.021), type of glycemic control (p=.021), stage of CKD (p=.003), and dialysis (p=.001). In the current study, CKD predicted reamputation after TMA and 30-day mortality. Our findings corroborate previous reports correlating dialysis-dependent renal failure and mortality. Whether patients in certain stages of CKD would achieve better outcomes with higher-level amputation rather than a TMA requires further study.

Figure.
Critical Regulation of Angiogenesis by Nrf2 Signaling Is Absent in Diabetic Wound Healing

PULI, S. RASBANAI, JOSHUA A. DAVID, DARREN L. SULTAN, ALVARO P. VIL-LAREAL-PONCE, JENNIFER KWONG, JASMINE LEE, CHEN SHEN, SALMA A. ABOU, DANIEL CERADINI, New York, NY

Diabetes-associated ulcers account for 11% of non-traumatic limb and extremity amputations. Tailoring therapies for chronic diabetic wounds is challenging. However, specific molecular/cellular events responsible for the extreme delays or lack of wound healing mostly remain at large. We previously identified dysfunction of the cytoprotective Nrf2/Keap1 signaling pathway induced by chronic hyperglycemia and diabetes. In the diabetic wound bed, we found detrimental impact on angiogenesis which is a requisitie for tissue repair. Exogenous activation of Nrf2 in the whole diabetic wound bed accelerated healing and illustrated the promise of targeting Nrf2 activity for reversing diabetes-associated impairments. Here, we explored the specific role of Nrf2 in endothelial cells of the wound tissue repair niche, and corresponding deficiencies in Nrf2 activity during diabetic wound healing. We generated Cdh5CreERT2;Nrf2lox/lox mice to deplete Nrf2 specifically in endothelial cells, upon tamoxifen administration (Nrf2KO mice). Stented excisional wounds (10mm diameter) on Nrf2KO mice, induced prior to wounding, required 33±1.23 days for closure. This delayed repair phenotype was significantly higher than that of wild type wounds requiring 14.5±0.29 days for healing, required 33±1.23 days for closure. This delayed repair phenotype was significantly higher than that of wild type wounds requiring 14.5±0.29 days for healing. This delayed repair phenotype was significantly higher than that of wild type wounds requiring 14.5±0.29 days for healing.

Conclusion that though surgical operation was a little bit more accurate than debridement, required 33±1.23 days for closure. This delayed repair phenotype was significantly higher than that of wild type wounds requiring 14.5±0.29 days for healing. This delayed repair phenotype was significantly higher than that of wild type wounds requiring 14.5±0.29 days for healing. This delayed repair phenotype was significantly higher than that of wild type wounds requiring 14.5±0.29 days for healing.

Supported By: American Diabetes Association/Pathway to Stop Diabetes (1-16-ACE-08 to D.C.)

Comparison of Microbiological Results of Two Bone Sampling Methods in Diabetic Foot Osteomyelitis—Debridement vs. Operation

MENGCHEN ZOU, PING HU, YANLING PAN, XANGRONG LUO, YA JIANG, YAO-MING XUE, YING CAO, FANG GAO, Guangzhou South

The purpose of this study is to compare the microbiological results of debridement bone samples with those of corresponding results of operation bone samples for patients with diabetic foot osteomyelitis, using 16s RNA high-throughput sequencing approach. We prospectively recruited 24 diabetic foot patients with osteomyelitis, and obtained 9 bone samples during surgery (Ds-Group) and 16 bone samples from debridement (Dd-Group). We compared the differences between debridement and operation procedures based on microbiological study of bone samples via 16s rRNA sequencing, using Ion PGM™ System Sequencer. It was obvious that microbes in Ds-Group, with narrower distribution, were more stable in alpha and beta diversity analysis. As for genera, totally 14 dominant genera were separated, and the average of Ds-Group and Dd-Group were respectively 10.44 and 9.44, with no statistically significant difference (P>0.05). Halomonas spp. and Prevotella spp. were the predominant genera of Ds-Group and Dd-Group respectively. Ds-Group had significant more Anaerococcus spp., Diaster spp. and Pseudomonas spp. than Dd-Group (P<0.05), but less Halomonas spp. and Nesterenokia spp. than Dd-Group (P>0.05). There were no differences in other dominant genera, such as Bacteroides spp., Finegilla spp., Fusobacterium spp., Parvimonas spp., Prevotella spp., Proteus spp., Staphylococcus spp., Streptococcus spp. and Veillonella spp. (P>0.05). We might draw a conclusion that though surgical operation was a little bit more accurate than debridement, microbiological study of bone samples from debridement could be capable enough for the diagnosis and treatment guidance of diabetic foot osteomyelitis.

Supported By: National Natural Science Foundation of China (81600648); Science and Technology Planning Project of Guangdong Province, China (2018B020200063, 2016ZC0086); Medical Science and Technology Research Foundation of Guangdong Province, China (A2017090)

Incidence and Risk Factors for Amputation in Patients with Diabet-Bone Sampling Methods in Diabetic Foot Osteomyelitis—Debridement vs. Operation}

635-P

Comparison of Microbiological Results of Two Bone Sampling Methods in Diabetic Foot Osteomyelitis—Debridement vs. Operation

MENGCHEN ZOU, PING HU, YANLING PAN, XANGRONG LUO, YA JIANG, YAO-MING XUE, YING CAO, FANG GAO, Guangzhou South

The purpose of this study is to compare the microbiological results of debridement bone samples with those of corresponding results of operation bone samples for patients with diabetic foot osteomyelitis, using 16s RNA high-throughput sequencing approach. We prospectively recruited 24 diabetic foot patients with osteomyelitis, and obtained 9 bone samples during surgery (Ds-Group) and 16 bone samples from debridement (Dd-Group). We compared the differences between debridement and operation procedures based on microbiological study of bone samples via 16s rRNA sequencing, using Ion PGM™ System Sequencer. It was obvious that microbes in Ds-Group, with narrower distribution, were more stable in alpha and beta diversity analysis. As for genera, totally 14 dominant genera were separated, and the average of Ds-Group and Dd-Group were respectively 10.44 and 9.44, with no statistically significant difference (P>0.05). Halomonas spp. and Prevotella spp. were the predominant genera of Ds-Group and Dd-Group respectively. Ds-Group had significant more Anaerococcus spp., Diaster spp. and Pseudomonas spp. than Dd-Group (P<0.05), but less Halomonas spp. and Nesterenokia spp. than Dd-Group (P>0.05). There were no differences in other dominant genera, such as Bacteroides spp., Finegilla spp., Fusobacterium spp., Parvimonas spp., Prevotella spp., Proteus spp., Staphylococcus spp., Streptococcus spp. and Veillonella spp. (P>0.05). We might draw a conclusion that though surgical operation was a little bit more accurate than debridement, microbiological study of bone samples from debridement could be capable enough for the diagnosis and treatment guidance of diabetic foot osteomyelitis.

Supported By: National Natural Science Foundation of China (81600648); Science and Technology Planning Project of Guangdong Province, China (2018B020200063, 2016ZC0086); Medical Science and Technology Research Foundation of Guangdong Province, China (A2017090)

636-P

Feasibility of Creating a Diagnosis-Based Diabetic Foot Registry in a Large Health Care Provider

AVIVIT CAHN, TALYA ALTARAS, TAL AGAMI, SR., ORI LIRAN, COLETTE E. TOUYAT, RENA POLLACK, ITAMAR RAZ, GHABRI CHIDICK, INBAR ZUCKER, Jerusalem, Israel; Rehovot, Israel; Petah Tikva, Israel; Alrod, Israel; Teli Aviv, Israel; Ramat Gan, Israel

We aimed to assess the validity of diagnostic codes relating to diabetic foot ulcer (DFU) in real-world data seeking to create a national DFU registry. Data were obtained from the diabetes registry of Maccabi Healthcare Service (MHS), a 2.1 million member sick fund in Israel, which included 122,500 patients in 2015. We randomly selected and reviewed ~400 patient files from each of the following categories: 1) had a diagnostic code of DFU in 2015; 2) had a diagnostic code suggestive of DFU in 2015 including: leg ulcer, amputation, DFU in proximate years or abnormality reported by nurse, 3) high risk patients (peripheral arterial disease (PAD), neuropathy, etc.). The patients’ charts were reviewed by study physicians and DFU was validated or refuted. Relying upon diagnostic codes entered by physicians, the positive predictive value was 73.1% (95% CI 67.6-78.2) and the sensitivity was 48.2% (95% CI 45.8-50.7%). We therefore conclude that the diagnostic codes alone cannot be relied upon to create a DFU registry, and a prospective registry is considered. The estimated annual prevalence of DFU in the diabetes registry of MHS in 2015 was 1.3% (95% CI 1.0-1.6%). Clinical features and outcomes of patients with validated diagnostic codes of DFU are shown (Table). In multivariate analysis age, diabetes duration, socioeconomic status, previous amputation and PAD were independently associated with risk of amputation or death.

Supported By: Medical Research and Development Fund for Health Services of Jerusalem

635-P

Comparison of Microbiological Results of Two Bone Sampling Methods in Diabetic Foot Osteomyelitis—Debridement vs. Operation

MENGCHEN ZOU, PING HU, YANLING PAN, XANGRONG LUO, YA JIANG, YAO-MING XUE, YING CAO, FANG GAO, Guangzhou South

The purpose of this study is to compare the microbiological results of debridement bone samples with those of corresponding results of operation bone samples for patients with diabetic foot osteomyelitis, using 16s RNA high-throughput sequencing approach. We prospectively recruited 24 diabetic foot patients with osteomyelitis, and obtained 9 bone samples during surgery (Ds-Group) and 16 bone samples from debridement (Dd-Group). We compared the differences between debridement and operation procedures based on microbiological study of bone samples via 16s rRNA sequencing, using Ion PGM™ System Sequencer. It was obvious that microbes in Ds-Group, with narrower distribution, were more stable in alpha and beta diversity analysis. As for genera, totally 14 dominant genera were separated, and the average of Ds-Group and Dd-Group were respectively 10.44 and 9.44, with no statistically significant difference (P>0.05). Halomonas spp. and Prevotella spp. were the predominant genera of Ds-Group and Dd-Group respectively. Ds-Group had significant more Anaerococcus spp., Diaster spp. and Pseudomonas spp. than Dd-Group (P<0.05), but less Halomonas spp. and Nesterenokia spp. than Dd-Group (P>0.05). There were no differences in other dominant genera, such as Bacteroides spp., Finegilla spp., Fusobacterium spp., Parvimonas spp., Prevotella spp., Proteus spp., Staphylococcus spp., Streptococcus spp. and Veillonella spp. (P>0.05). We might draw a conclusion that though surgical operation was a little bit more accurate than debridement, microbiological study of bone samples from debridement could be capable enough for the diagnosis and treatment guidance of diabetic foot osteomyelitis.

Supported By: National Natural Science Foundation of China (81600648); Science and Technology Planning Project of Guangdong Province, China (2018B020200063, 2016ZC0086); Medical Science and Technology Research Foundation of Guangdong Province, China (A2017090)
The Leucopatch® System in the Management of Hard-to-Heal Diabetic Foot Ulcers—A Multicentre, Multinational, Observer-Blinded, Randomised Controlled Trial

Methods: 595 people with diabetes and a foot ulcer consented to participate. After a 4 week run-in-period those with a reduction in ulcer area of < 50% were randomised to either pre-specified good standard care alone or the intervention group (p=0.0246) (Figure). No difference in adverse events within 20 weeks vs. 21.6% (n=29/134) of the controls (OR 1.58, 95% CI 1.06-2.35; p=0.02) by intention-to-treat analysis. Time to healing was shorter in the intervention group (p=0.0246) (Figure). No difference in adverse events was seen between groups.

Interpretation: The use of Leucopatch® is associated with significant enhancement of healing of hard-to-heal foot ulcers in people with diabetes.

Justification: Our results implied large differences in incidence and risk profiles for amputation in Japanese patients with diabetes, suggesting the need for ethnic group-specific strategies to prevent diabetic foot disease.

Figure.

<table>
<thead>
<tr>
<th>Leucopatch® Ulcer Care</th>
<th>Days to Healing</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>50</td>
<td>1</td>
</tr>
<tr>
<td>100</td>
<td>2</td>
</tr>
<tr>
<td>150</td>
<td>3</td>
</tr>
</tbody>
</table>

Supported by: Reapplix ApS
The Roles of NLRP3 Inflammasome and ADAR1 in Diabetic Foot Ulcer

FANG WANG, LIULING ZHAO, WENJUN YANG, HONGHUI HE, ZHAOHUI MO, Changsha, China

Infected diabetic foot ulcer (DFU) is an important problem because it is a limb or even life threatening, and burdens a great financial load to the community. It’s shown that circulating inflammatory proteins are reputed to be of poor value for diagnosing DFU as lack of specificity. Therefore it’s necessary to investigate newer discussed inflammatory parameters. NLRP3 inflammasome, a multiprotein complex consists of NLRP3, ASC and pro-caspase-1 and controls the production of IL-1β and IL-18, is an important contributor to the development of type 2 diabetes. The RNA-specific adenosine deaminase (ADAR1) is interferon-inducible double stranded (ds) RNA-binding protein, which is demonstrated to inhibit the production of type 1 interferons and various proinflammatory cytokines such as TNF-a and IL-6. But little is known about the ex vivo profile of NLRP3 inflammasome and ADAR1 in DFU. On this basis the aim of our study was to evaluate the role of NLRP3 inflammasome and ADAR1 in subjects with DFU in comparison with subjects without DFU. We completed a study including 20 healthy volunteers, 20 newly diagnosed type 2 diabetic (T2D) patients and 30 DFU patients (wagner2-4). When compared to NDW (p<0.04), DW showed a 75% reduction in nuclear Nrf2 protein expression (p<0.02) as compared to NDW. DW also exhibited a 25% relative reduction in gene expression of MnSOD, a key Nrf2 downstream antioxidant enzyme, and 5-fold decrease in epidermal nuclear Nrf2 protein expression (p<0.01), which are comparable to NDW. DW also exhibited a 25% relative reduction in gene expression of MnSOD, a key Nrf2 downstream antioxidant enzyme, and 5-fold decrease in epidermal nuclear Nrf2 protein expression (p<0.01). Hence, we implicate Nrf2 dysfunction in impaired redox homeostasis and consequent oxidative damage in both human diabetic skin and diabetic wounds as compared to nondiabetics. We also identify Keap1 as a likely mediator of impaired healing in diabetic wounds. These results recapitulate our previous findings in mice, further validating this critical pathway as a promising target for understanding and treating diabetic wound healing.

Supported By: National Natural Science Foundation of China
in admission time. The diagnosis of osteomyelitis was made with MRI, RX, probe-to-bone test and verification of elevated ESR and CRP. We start with the collection of the cultures (bone sample in 8 of 28 patients) and antibiotic treatment according the cultures. After the diagnosis of osteomyelitis we proceeded to prepare a surgical field and through the ulcer we removed the infected bone-phaalanx taking a biopsy sample for microbiological study. After we scraped and cleaned the cavity well, a 48-hour drain was placed and becomes transdermal wound suture if is a necessary. The duration of the antibiotic treatment depends from the lesion area, the results of microbiological culture and varies from 4-6 weeks to 4-6 months.

Results: After practicing this technique all cases were healed at an average 40 days with an effective offload and an appropriate topical care to keep the ulcer clean and with an optional moisture. The duration of hospitalization 2-8 days depending on the severity of the infection.

Conclusion: It is essential to raise other less invasive and conservative methods than amputation. Specially in those with good distal arterial perfusion that in many cases are young, the avoidance of a amputation has many benefits in their quality of life. Finally, the applied method is rapid inexpensive without disturbing the biomechanical balance of the foot to a large extent.

Osteomyelitis and Neuropathic Ulcers in Forefoot—Amputation Is the Only Surgical Intervention Resolving?

DIМИТΡΗΣ ΣΚΟΥΤΑΣ, ΤΑΡΗΣ ΣΑΒΕΓΗ, ΣΥΜΕΟΝ ΜΕΤΑΛΛΙΔΟΣ, ΣΩΚΡΑΤΗΣ ΣΙΟΥΤΖΑΚΟΣ, ΙΩΑΝΝΗΣ ΚΑΤΣΙΝΟΣ, ΘΑΜΑΤΑ ΓΕΩΡΓΙΑ, ΑΘΑΝΑΣΙΟΣ ΝΙΚΟΛΑΙΔΗΣ, ΣΡ., ΛΟΥΚΑΣ ΔΟΥΚΑΣ, JR., ΕΛΕΝΑ ΜΑΤΟΠΟΥΛΟ, ΣΟΛΟΜΟΝ ΤΕΣΣΑΥ, ΧΡΙΣΤΟΣ ΜΑΝΕΣ, ΓΛΥΚΕΡΙΑ ΤΖΑΤΖΑΓΟΥ, Θεσσαλονίκη, Ελλάδα, Σουφλί, Ηνωμένο Βασίλειο

Background and Aim: The aim of this study is to show a simple therapeutic method in cases of neuropathic ulcer complicated by osteomyelitis in the forefoot to resolve this complication avoiding amputation.

Patients-Methods: Our material consists of 28 patients (19 males, 9 females) with “diabetic foot” aged 57.3±10.25 years, mean HbA1c: 8.65±1.7%, of duration of diabetes 13.84±9.2 years and 32% of them are active smokers. NDS, VPT, ABI are measured. All of them had neuropathic ulcers located in the forefoot and 10 of them had previous amputations. The average duration of the ulcer was 1 year complicated with osteomyelitis

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>Diabetes Foot Wound Healing—A Collaborative Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Authors</td>
<td>JACQUELINE N. MCNULTY, BRANDON J. LEWIS, JAVIER LA FONTAINE, APRIL ROSE, MIRIAM GOMEZ, LUIGI MENEGHINI, UMA GUNASEKARAN, MARIA S. RUIZ, Dallas, TX</td>
</tr>
<tr>
<td>Summary</td>
<td>There exists limited data demonstrating that glycemic control can improve healing of diabetic foot wounds. From March through December 2017, patients followed in the Foot Wound Clinic of a large urban safety net health system were concurrently seen by diabetes specialists to determine whether improving glycemic control via an integrated treatment approach impacted wound healing. This pilot study is the first to examine the effect of diabetes specialty co-management with podiatric care of diabetic foot wounds. Sixty patients were included in the analysis of this pilot program and were followed for an average of 220 days. Patients were classified as having either improved glycemic control (IGC) or non-improved glycemic control (NIGC) defined as &lt;1% HbA1c change at study end. Cohort characteristics and outcomes are summarized in Table 1. All patients had aggressive diabetic foot care including wound debridement and appropriate antibiotic therapy as determined by their podiatrist. Ulcers worsened in 47% of NIGC patients compared to 13% of IGC patients with IGC patients having an average HbA1c reduction of 2%. With both NIGC and IGC groups receiving similar wound management, 63% of NIGC patients had decreased ulcer volume compared to 87% of IGC patients, suggesting that improving glycemic control, in collaboration with diabetes specialist co-management, contributes to improved wound healing and a trend for decreased resource utilization.</td>
</tr>
</tbody>
</table>
Background and Aim: The aim of this study is to show a simple therapeutic method in cases of neuropathic ulcer complicated by osteomyelitis in the foot to resolve this complication avoiding amputation.

Patients- Methods: Our material consists of 28 patients (19 males, 9 females) with “diabetic foot” aged 57.3±10.25 years, mean HbA1c: 9.6±5.1%, of duration of diabetes 13.8±12.2 years and 32% of them are active smokers. NDS, VPT, ABI are measured. All of them had neuropathic ulcers located in the foot and 10 of them had previous amputations. The average duration of the ulcer was 1 year complicated with osteomyelitis in admission time. The diagnosis of osteomyelitis was made with MRI, RX, probe-to-bone test and verification of elevated ESR and CRP. We start with the collection of the cultures (bone sample in 6 of 28 patients) and antibiotic treatment according the cultures. After the diagnosis of osteomyelitis we proceeded to prepare a surgical field and through the ulcer we removed the infected bone-phalanx taking a biopsy sample for microbiological study. After we scraped and cleaned the cavity well, a 48-hour drain was placed and becomes transdermal wound suture if is a necessary. The duration of the antibiotic treatment depends from the lesion area, the results of microbiological culture and varies from 4-6 weeks to 4-6 months.

Results: After practicing this technique all cases were healed at an average 40 days with an effective offload and an appropriate topical care to keep the ulcer clean and with an optional moisture. The duration of hospitalization 2-8 days depending on the severity of the infection.

Conclusion: It is essential to raise other less invasive and conservative methods than amputation. Specially in those with good distal arterial perfusion that in many cases are young, the avoidance of a amputation has many benefits in their quality of life. Finally, the applied method is rapid inexpensive without disturbing the biomechanical balance of the foot to a large extent.

Table 1. Cohort Characteristics and Study Outcomes.

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>IGC</th>
<th>NIGC</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of patients</td>
<td>30</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Total No. of ulcers</td>
<td>38</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Median ulcer size (mm²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>170</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Study End</td>
<td>0</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Patients with improved ulcer healing, n (%)</td>
<td>26 (87)</td>
<td>19 (63)</td>
<td>0.04</td>
</tr>
<tr>
<td>HbA1c, mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>10.6</td>
<td>10.2</td>
<td>0.47</td>
</tr>
<tr>
<td>Study End</td>
<td>8.2</td>
<td>11.1</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preexisting</td>
<td>25 (83)</td>
<td>24 (80)</td>
<td></td>
</tr>
<tr>
<td>Controlled at baseline</td>
<td>19 (63)</td>
<td>16 (53)</td>
<td></td>
</tr>
<tr>
<td>Controlled at study end</td>
<td>19 (63)</td>
<td>21 (70)</td>
<td></td>
</tr>
<tr>
<td>ED visits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total visits</td>
<td>35</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Average No. of visits per patient</td>
<td>1.9</td>
<td>2.3</td>
<td>0.19</td>
</tr>
<tr>
<td>Foot related</td>
<td>10</td>
<td>26</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes related</td>
<td>4</td>
<td>2</td>
<td>0.38</td>
</tr>
<tr>
<td>Average number of podiatric appointments</td>
<td>5</td>
<td>7</td>
<td>0.92</td>
</tr>
<tr>
<td>No. of patients seen by Diabetes specialist</td>
<td>25</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Average No. of specialist visits per patient</td>
<td>2.3</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>No. of patients seen in co-management visit</td>
<td>25</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>No. seen in sporadic visit</td>
<td>0</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>No visits</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

Lost to follow-up with diabetes specialist, n (%) | 13 (43) | 15 (50) | 0.38 |

Employee Health: Diabetes Self-Management with Wireless Technology
JOHN BRUCH, MICHELLE D. STANCIL, JESSICA M. ODIM, BRYCE A. NELSON, LINDSAY S. REUBACH, REBECCA RUSS-SELLERS, ALYSON GHIZZONI BURNS, MAINE R. LINDHOLM, JONDA DAWSON, NATHAN A. SCHWECKE, GREENVILLE, SC
In 2014, Greenville Health System spent more than double on employees with A1c greater than 7.5% compared to employees with A1c less than 7.5%. Visits with a primary care physician every three months may be inadequate to meet the needs of a patient with uncontrolled diabetes. The goal of the study was to improve care for a targeted population of employees of a large health care system with type 1 or 2 diabetes. The intervention combined diabetes education, telehealth, a wireless enabled meter, and algorithms for medication adjustments.

Methods: Fifty patients were given a wireless enabled meter that links to secure portal for the healthcare professional, the patient, and a support person. The primary objective was to achieve a ≥5 percent reduction in patients’ average baseline A1c. Secondary objectives included improving patient’s understanding of diabetes and self-management of diabetes, increasing adherence rates of diabetes monitoring and medication utilization, decreasing rates of hypoglycemic or hyperglycemic events, and reduce overall cost of healthcare. Patients were contacted by a diabetes educator every 2-4 weeks. A medication algorithm was used to titrate insulin and noninsulin medications and initiate additional treatments.

Results: Patients were followed for an average of 27.6 months. Baseline A1c average of 10.24% was reduced to an average of 8.39% (absolute reduction of 1.856 or 18% reduction from baseline). Compared to baseline, at 12 months patients reported improvement in their self-rated diabetes knowledge, self-monitoring behaviors, and self-management behaviors. Participants increased their outpatient visits with primary care providers and Endocrinology. Average cost for both endocrinology and PCP visits decreased from pre-enrollment to 10%.

In conclusion, by combining diabetes education, medication algorithms, and remote glucose monitoring, patients improved their knowledge of diabetes and self-care and experienced improved glyemic control.

Diabetes Knowledge and Numeracy among Under- or Uninsured Latinos with Type 2 Diabetes
YA-CHING HUANG, ALEXANDRA A. GARCIA, JULIE A. ZUNIGA, AUSTIN, TX
For people with diabetes, low literacy and low numeracy are risk factors for poor diabetes outcomes. Diabetes Numeracy is a predictor of diet management and A1C. The purpose of this study was to analyze the relationship between diabetes knowledge and numeracy in Latinos with type 2 diabetes (T2DM). Participants (n=139) from 3 clinics for un- and underinsured people completed the Spoken Knowledge in Low Literacy for Diabetes (SKILLD, 11 open-ended items, possible scores = 0-11), Diabetes Knowledge Questionnaire (DKQ, 24 true-false items, possible scores = 0-24), and a short version of the Diabetes Numeracy Test (DNT, 5 open-ended items, possible scores = 0-5); higher scores indicated better knowledge or numeracy. We calculated descriptive and correlational statistics and estimated hierarchical regression models in diabetes numeracy with these sets of predictors: (1) demographic (age, gender, married, education, and acculturation); (2) SKILLD, DKQ, and DNT scores. Participants were predominately middle-aged (mean 48.3 ± 9.324 years), female (62.5%), married (65.5%), with an average of 9.13 years of education ± 4.62. Mean SKILLD score = 6.45 ± 1.95 (95% correct); DKQ score = 16.63 ± 2.81 (89%); and DNT score = 1.91 ± 1.31 (28%). Years of education, SKILLD, and DKQ score were positively correlated to DNT scores. However, after controlling for demographic characteristics, only education and DKQ score were significant predictors of DNT scores in the hierarchical regression model. People with higher education level and DKQ score had an increase in all DDS-17 domains at the completion of Class 4; however, by 6 months, distress returned to baseline levels. Patient satisfaction surveys were completed at DCOE (n=429) and RAFB (n=227) at each encounter and provider satisfaction surveys were collected from RAFB facilitators. Patients at RAFB reported higher satisfaction (99.1%) than DCOE patients (97.2%). In fact, most measures of satisfaction were higher in RAFB patients than DCOE patients. Moreover, facilitators expressed high satisfaction with DSME via MIST and all facilitators were willing to conduct more classes in this format. Initialization of the DSME Telehealth program presented challenges, especially in technology-related issues and documentation at 6 months. The pilot program allowed the DCOE to gain valuable feedback from our remote site. Technology issues have largely been resolved enabling us to provide an even better experience to our new sites in 2018.
Reported higher DNT. The entire regression model accounted for 25.7% of variance in DNT (F = 6.42, p < .001). Participants in this study had low diabetes knowledge and very low numeracy. Focusing on numeracy (e.g., using food labels, calculating portion size, and interpreting medication labels), especially for the least educated, may provide the most benefit in behavior and outcomes. Future studies should examine numeracy as it relates to self-management behaviors and outcomes.

Supported By: University of Texas at Austin School of Nursing

To Puedes—An Exploratory Usability Pilot of a Postpartum Education “App” for Latina Women with Previous Gestational Diabetes

KRISTIN CASTORINO, SILVIA ALVAREZ, HANNAH M. MATHERS, ARIANNA J. LAREZ, CEARA AXELROD, Santa Barbara, CA

Diabetes gestational mellitus (GDM) affects nearly 14% of Latina women—a rate significantly higher than the background population. Standard-of-care dictates that postpartum education should be provided though it is rarely done due to socioeconomic, linguistic, transportation and childcare barriers. We propose that a smartphone application (app) has the potential to serve as a cost-effective approach to delivering health education that can break through these barriers and empower postpartum Latina women with the education requisite for making positive lifestyle changes. We designed a small pilot study to test the app’s usability to inform larger studies. Tu Puedes is a culturally and linguistically appropriate diabetes prevention app we developed in Spanish. Women with previous GDM aged 18-40 years completed 4 lessons, either through the app or via an in-person classroom setting with a scripted curriculum. A pre- and post-survey was given to assess participants’ qualitative experience using the app. In addition, standard metabolic measures at baseline and post-intervention (4 weeks) were completed, and compared for both groups. Of the 22 women recruited, 17 completed all 4 lessons, with greater retention in the app group. Survey responses were overall positive, with 73% of participants deeming the app both easy to use and better than any past group education. Users had a 40% increase in self-perceived health, 67% of users wanted to continue use of the app, and all users would recommend it to a friend. Though insufficiently powered and for nominal duration, we found significant decreases in weight and BMI compared to the control group with 90% and 95% confidence respectively, but not in blood pressure or waist circumference. Our results suggest that the Tu Puedes app is a feasible and user-friendly way to disseminate postpartum diabetes prevention education to a Spanish-speaking Latina population with previous GDM, and support the need for further research.

Moderated Poster Discussion: Targeting People and Educational Barriers to Improve Outcomes (Posters: 654-P to 659-P), see page 19.

Barriers and Facilitators to Perceived Diabetes Self-Management in Arab Americans with Diabetes

DANA D. MASHKAR, DEBORAH PIATT, NIKOLAS J. KOSCIEJ, LINDA JABER, Detroit, MI, Ann Arbor, MI

Arab Americans (AAs) are at increased risk of type 2 diabetes, with a reported prevalence of 18%. Despite the increasing prevalence, there remains a lack of data on diabetes self-management (DSM) practices and barriers to care in this population. The purpose of this study was to assess patient perceptions of DSM behaviors in order to facilitate individualized care plans by providers. A 39-item survey was created based on focus group discussions designed to understand the impact of AA culture on DSM. The survey assessed diet, adherence to medications, exercise, healthy lifestyle, and family support. Two hundred AAs with diabetes completed the survey via face-to-face interviews. Most participants were above fifty years of age (79%), females (59%), and originated from Lebanon (73%). Individuals receiving Arabic instructions perceived that good portion control (p=0.07), food selection (p=0.01), and maintaining a healthy lifestyle (p=0.003) were important DSM behaviors, compared to those who did not receive Arabic instructions. Unemployed individuals were less likely to perceive regular exercise (p=0.05), portion control (p=0.06), and maintaining a healthy lifestyle (p=0.08) as important DSM behaviors compared to employed individuals. Individuals who had family support and encouragement were more likely to perceive that discussions with their clinicians were important (p=0.003) compared to those without family support. Individuals with family who understood their food choices were more likely to perceive regular exercise (p=0.03) as important compared to those with families who did not understand food choices.

In conclusion, this survey may serve as a valuable tool for providers to assess perceptions surrounding DSM behaviors in order to provide patient-centered care that will help to improve patient outcomes. This study supports the importance of integrating cultural influences into DSM education and support when providing care to a population with a strong cultural identity.

Can Practice Redesign Improve Diabetes Self-Management Education (DSME) Referrals?

JODI KRALL, JUSTIN KANTER, VINCENT C. ARENA, KRISTINE RUPPERT, FRANCIS X. SOLANO, JR., LINDA M. SIMINERIO, Pittsburgh, PA

DSM is considered an essential component of diabetes care, but participation is abysmal. Referral processes and traditional delivery models may serve as barriers. The purpose of this study was to deploy a model that relied on elements of the patient-centered medical home (PCMH) and direct delivery of DEs in primary care (PC) and evaluate its impact on PC provider (PCP) referrals to DSME.

Methods: Using a non-randomized controlled design, DEs and PC practices were assigned to the intervention group (IG; 3 DEs, 6 practices) or control (2 DEs, 6 practices). Practices in the IG were introduced to DSME Position Statement (PS) referral algorithm and PCMH elements and negotiated application for their practice, including frequency of direct delivery of DSME in PC. Traditional DSME delivery (no direct link between DE and PC) served as control. To examine DSME referrals, data were extracted from medical records for all patients with DM, age 18-75y, who presented to their PCP over 12 months (n=4,508; 60.7% IG) and compared between study groups. Results: Mean age was 59.8y, and primarily male 51.2%. The IG referred a higher percentage of patients compared to the control group (12.6% vs. 7.9%; p<0.0001). Using logistic regression modeling, it was found that after adjusting for age, gender, race, A1C, obesity, and micro/macrovacular comorbid conditions, the IG was 1.9 (Confidence Level 1.5-2.4) times more likely to refer patients to DSME. Other factors found to predict referrals were female (Odds Ratio:1.3, CI 1.1 – 1.6), obesity (OR:2.7, CL 2.2-3.3) and

Moderated Poster Discussion: Targeting People and Educational Barriers to Improve Outcomes (Posters: 654-P to 659-P), see page 19.

Results of a Culturally Tailored Multidisciplinary Intervention on Diabetes Self-Care and Glycemic Outcome in Lebanese Patients with Type 2 Diabetes

OLA SUKKARIEH-HARAY, MAYA BASIL, LEONARD E. EGEBE, Byblos, Lebanon, Beirut, Lebanon, Milwaukee, WI

Background: Enhancing diabetes self-care is known to improve glycemic control of patients with type 2 diabetes mellitus (T2DM). According to American Diabetes Association guidelines, a multidisciplinary and culturally appropriate intervention is needed for optimal diabetes self-care and glycemic outcomes. There is no published study that evaluated an educational intervention targeting diabetes self-care and glycemic outcomes in Lebanese patients with T2DM.

Aim: The aim of this pilot-study was to test the effect of culturally-tailored educational program targeting diabetes self-care on glycemic control of Lebanese patients with T2DM, of low socioeconomic status.

Methods: A sample of 27 adults (Age: 51±0 years, 59% males, A1C 8.9±1.38%) diagnosed with T2DM for at least one year was recruited from two dispensaries in Beirut. Participants received culturally-tailored, multidisciplinary educational sessions based on the Information-Motivation-Behavioral model and on American Diabetes Association’s National Standards for Diabetes Self-Management Education and Support. Summary of Diabetes Self-Care Activities (SDSCA), Social Support Scale (SS), Diabetes Fatalism Scale (DFS), and Diabetes Knowledge Test (DKT), as well as blood samples (HbA1c, Fasting Plasma Glucose) were collected at baseline and three months post-intervention.

Results: Results revealed improvements in various diabetes self-care activities (Diet and Self-Monitoring Blood Glucose) after 3 months, which was reflected in a significant decrease in glycaemia (A1C: -0.6%; Fasting Plasma Glucose: -35 mg/dL; p<0.05).

Conclusion: This is the first intervention study showing the effectiveness of a culturally-tailored, multidisciplinary education program in improving glycemic control and diabetes self-care behavior of Lebanese patients with T2DM. It sets the stage for larger scale implementation with more representative sample.

Supported By: Lebanese American University

656-P

ADA-Supported Research

655-P

Supported By: Lebanese American University

654-P

Supported By: University of Texas at Austin School of Nursing

653-P
Parents with Type 1 Diabetes—Children’s Role in Self-Management

JODI KRALL, VICKI HELGESON, MEREDITH VAN VEEL, EUNJIN LEE, MARY-JANE SIMMS, MARY T. KORYTKOWSKI, CYNTHIA BERG, Pittsburgh, PA, Salt Lake City, UT

Family members are a potential resource to support DM self-management, but how children are involved in their parents’ T1DM has not been well explored. The purpose of this study was to examine parents’ perceptions of the role children play in their DM care. Young, middle-age, and older adults with T1DM (n=85) and their romantic partners (n=55) participated in interviews during which they described their children’s knowledge and involvement in DM care. Interviews were transcribed and responses coded. All parents reported that children knew of their DM, which they learned about progressively from a young age, first being aware of blood glucose (BG) checks and devices. Some parents felt that children, particularly younger ones, detracted from DM management on occasion (e.g., nursing infant, caring for busy toddlers), but this was usually transient. Conversely, parents reported children to be accepting and understanding of the ways that DM affected their family experiences (e.g., pause to check and/or treat low BG), while also taking on a level of responsibility or concern (e.g., carrying a snack for treatment, worry about driving). Regardless of child age, many parents did not want DM to burden children and limited their involvement in DM care. When asked about DM-related behaviors, parents rated “making parent feel better about DM” as the most frequently occurring behavior. Only 3% of parents who used continuous glucose monitors and/or insulin pumps (n=60) said that children received notifications. Almost 40% of parents (n=53) expressed concern that children would develop DM. Parents, and more so partners, requested resources to enhance child awareness and preparedness to support parents with DM as well as ways to learn how to better communicate as a family and share perspectives on how DM affects individual family members. Diabetes educators should consider developmentally and relationally appropriate ways to engage children of parents with T1DM in education and self-management.

Supported By: National Institute of Diabetes and Digestive and Kidney Diseases

657-P

Diabetes Self-Management Education Program Effect on Glycemic Control and Insulin Dosing in Poor Diabetes Literacy Patients from Urban Areas in Mexico City—Therapeutic Education Underuse and Insulin Overuse

RUBEN S-rA-rN- R, DANIELA G. MEZA, DAVID GARCIA MARTINEZ, JAVIER GROCO, ROCIO GARCIA, ELENA RIMERO, BANDEIJUN, VIRIDiana A. DE LA TORRE-SALDAN, JESUS A. RAMOS GARCIA, MARIA C. DOLORES, ENEDINA TERESA CUATECO-T, Mexico City, Mexico

Limited evidence exists on the efficacy of Diabetes Self-Management Education (DSME) in primary care urban population in low- and middle-income countries. This study evaluated the effect on glycemic control and insulin dosing in patients who attended an interdisciplinary educative structured program at Clínica Especializada en el Manejo de la Diabetes en México City, Iztapalapa in 2017. Intervention lasted 5 months and included individual and group sessions in a shared medical appointments model aimed at promoting self-care. In 252 patients with type 2 diabetes, diabetes literacy and self-care activities were assessed from the 10-item Spoken Knowledge in Urban Areas in Mexico City—Therapeutic Education Underuse and Insulin Overuse.

In 658-P

ADDA-Supported Research  Moderated Poster Discussion

658-P

Effects of a Primary Care-Based Chronic Care Model on Diabetes Self-Management, Diabetes Distress, and Health Care Experience

ADRIAN L. FORTMAN, JESSICA L. PRECADO, CHERI WALKER, ROBIN MUR-RIEY, KELLY BARGER, DETRIDE MILLS, MARIE ROBACKER, ATHENA PHILIS-TSAGAS, ASA, San Diego, CA

 postal, telephone, and in-person visits. To date, 23 patients have completed the study. No adverse events were reported. For this pilot study, we focused on addressing the barriers to patient engagement and self-management in the primary care setting, by developing and implementing a CCM-based diabetes management program that targets patients with low literacy, type 2 diabetes, and no prior treatment for T2DM.

658-P

Promoters of and Barriers to Engagement in Type 2 Diabetes Mellitus (T2DM) Populations with Real-World Technological Interventions

KEVIN R. DUVAI, ANJALI TRASY, ERIN MURRAY, ROBERT MILAS, TOBIAS SAVRE, ANNE C. EAL, Bridgewater, NJ

Glycemic control is often complicated by patients’ lack of adherence to treatment regimens and suboptimal self-efficacy behaviors. New technological interventions can help self-management, but it is often difficult to engage patients and maintain use. A systematic literature review of Medline, Embase, Cochrane CENTRAL, and manual searching identified literature reporting on technological interventions for T2DM to evaluate patient satisfaction affecting adherence. Observational studies and pragmatic clinical trials reporting intervention adherence and patient experience were evaluated for perceived promtions or barriers of intervention. The search retrieved 329 publications. Fourteen met criteria for inclusion and were analyzed. Adherence rates varied, ranging from 32-90% in web-based programs, to 28-90% in telemedicine programs. Shorter follow-up times generally indicated better adherence. Patient-specific feedback was reported for 1,000 patients in 11 studies. Common patient-reported promoters of initiation and adherence included high level of provider interest, motivating, encouraging and person-ally relevant educational messaging. Barriers for the interventions included lack of motivational messaging, educational value, redundancy, technology-related limitations and overload concern. Technological interventions such as smartphone applications and patient web portals offer an opportunity to increase self-management in T2DM, further aided by strong healthcare provider promotion, support and engagement. In developing new technological interventions, it is important to consider easy-to-use individually-tailored content that is both motivational and educational. These programs will offer the best opportunities for adoption by providers and improved self-management by patients. Further review is needed to identify which technological interventions are most efficacious.

Supported By: Sanofi

660-P

ADA-Supported Research  Moderated Poster Discussion
Multidisciplinary Pre-Pregnancy Team Education for Patients with Diabetic Nephropathy Reduced Cost for Admission in the Reduction of Hemodialysis, and Subsequent Mortality

MAMIKO HITOMI, TERIKO SATO, TATSUMI MORIYAMA, Sagamihara, Japan, Tokyo, Japan

Although a multidisciplinary individual team approach (MTA) has been thought to help prevent the progress of diabetic nephropathy (DN), its efficacy has not been fully examined. We compared the effect of an MTA on the hemodialysis (HD) course of 51 DN patients with that of 34 DN patients managed via a dietician approach (DA) alone (total patients, n=85; male, n=58; age, 62±12 years; T2DM, n=81). In all cases, HD was initiated between January 2010 and May 2016. MTA staff members were doctors, dietitians, nurses, laboratory technologists, and pharmacists. Each intervention took 15–30 min at an outpatient clinic on the day of doctor visits. The team provided advice on nutrition, medication, medical exam, foot care, self-monitoring, and self-management. In the MTA group, the annual number of intervention sessions was higher, the cardiothoracic ratio was lower, and the cost per admission for HD induction was lower in comparison to the DA group (5.0±5.5/year vs. 2.0±2.0/year; P=0.004; 53.1±6.6% vs. 57.3±7.4%, P=0.009; and 1.55±0.85 vs. 2.04±0.15 million JPY; P=0.029). Four patients in the MTA group and 9 in the DA group died during the observation period (likelihood ratio 5.381, P=0.020). A Kaplan-Meier survival analysis showed that the MTA group had superior patient survival (log rank P=0.009). The number of patients who underwent 24-h corrected urine tests 6 months before HD was higher in the MTA group (n=20 vs. n=5; likelihood ratio 6.281, P=0.025), while the urinary sodium excretion in 24 h urine collection was lower in the MTA group (8.2±2.2 g/day vs. 13.0±6.9, P=0.011). The stepwise regression analysis showed that the MTA and DA classifications mostly affected patient survival at the final observation (F=7.20, P=0.014).

In conclusion, the MTA provided good clinical and economic results for DN patients through improved self-management and an improved clinical course, even when implemented after the initiation of HD.

A174

Feasibility of Mother-Daughter Dyadic Gestational Diabetes (GDM) Risk Reduction Intervention for American Indian and Alaska Native (AIAN) Teens

KELLY R. MOORE, SARAH A. STOTZ, KRISTEN J. NADEAU, SUSAN M. SEREKA, YESENA GARCIA REYES, HOWARD R. STEIN, DENISE CHARRON-FRUCHNOWIK, Aurora, CO; Pittsburgh, PA

AIAN women have twice the risk compared to the general U.S. population of adolescent obesity, pregnancy, and GDM. Stopping GDM (SGDM), a GDM risk reduction intervention tailored for at-risk AIAN teens, is based on a validated preconception-counseling program, READY-Girls. Prior to starting a multi-tribal randomized controlled trial (RCT) to test SGDM’s effectiveness, a feasibility study was conducted in Denver, CO with AIAN participants (4 mothers, 5 daughters). Mother-daughter (M-D) dyads were recruited through an Urban Indian Health program. Daughters were at risk for GDM as assessed by BMI >85th percentile and did not have diabetes based on finger-stick HbA1c < 5.5%. Mother’s (M) mean age was 44.4±8 years and 100% had some college education; daughter’s (D) mean age was 15.9±2.7 years and 80% were <12th grade. A pre-post online questionnaire evaluated the 2-hour online intervention which included viewing the electronic SGDM book and video. Outcomes included knowledge about GDM, reproductive health and healthy lifestyle, self-efficacy, and satisfaction with the eBook and video. Post-open-ended questions revealed that participants had concerns about the font size and length of the materials and enjoyed the video; could relate to the stories, images, and actors; and appreciated learning about GDM specific to AIAN women. Mean pre- to post-knowledge increased for both mothers and daughters on diabetes prevention (M 70% to 80%; D 42% to 60%) and productive health and GDM knowledge (M 65% to 92%; D 34% to 71%). Mothers also demonstrated increased self-efficacy for healthy living and pregnancy planning. The eBook, video, and website were scored moderately high to very high on satisfaction.

In conclusion, we determined that the SGDM intervention is feasible and acceptable in AIAN M-D dyads. These findings will be used to finalize the SGDM education materials and data collection protocol for the upcoming full-scale RCT.

Supported By: National Institutes of Health/National Institute of Nursing Research (R01NR014621-01A).
An Evaluation of the Diabetes Conversation Map Program—Health Outcomes and Health Care Utilization during a Four-Year Follow-Up

EINAV SRLUDVCI, MAYA LEVENTER-ROBERTS, BRADLEY CURTIS, XUANYAO HE, MOSHE B. HOSHEN, MINA RITEM, ILAN GOFER, EFRAT SHADMI, CALANIT KEY, NOMY LEVIN-JANA, ALENA STRIZEK, BECCA S. FELDMAN, Haifa, Israel; Tel Aviv, Israel; Sydney, Australia; Indianapolis, IN; Rishon Le Zion, Israel; Raanana, Israel

Background: The Diabetes Conversation Map™ (Map™) is a global education program that engages patients with type 2 diabetes Mellitus (T2DM) in group-based discussions on diabetes-related topics. This study compares outcomes annually between participants and matched controls over a 4-year period.

Methods: This was a retrospective cohort study of 11,053 Clalit Health Services members with T2DM who enrolled in the Map™ program between 1.1.2010 and 4.1.2016. The associations between program participation and annual laboratory test results (HbA1c, glucose and LDL levels), health behaviors (frequency of glucose and HbA1c testing), and healthcare utilization (hospital, physician and specialist visits) were assessed between cases and controls using regression analysis.

Results: The Map™ group had significantly improved HbA1c, glucose, and LDL levels and more frequent blood glucose testing each year up to 36 months post-enrollment compared to matched-controls. They also had significantly fewer annual primary care visits but more annual ophthalmologist and nutritionist visits up to 24, 36, and 48 months post-enrollment, respectively, compared to matched-controls. The annual frequency of hospital admissions and length of hospital stay was lower up to 36 and 48 months post enrollment, respectively, in the Map™ group compared to matched-controls.

Conclusions: Participation in the Map™ program was associated with improved clinical outcomes, behaviors, and healthcare utilization for at least 24 months, suggesting that an intervention booster may be needed beyond this time period. These findings support the significant impact of the Map™ program on the lives of patients with T2DM.

Supported By: Eli Lilly and Company

An Evaluation of the Diabetes Conversation Map™ Program—Are Program Factors Associated with Health Outcomes and Health Care Utilization at 12 Months Post-Enrollment?

EINAV SRLUDVCI, MAYA LEVENTER-ROBERTS, BRADLEY CURTIS, XUANYAO HE, AMICAY ARAKI, MOSHE B. HOSHEN, MINA RITEM, ILAN GOFER, EFRAT SHADMI, CALANIT KEY, NOMY LEVIN-JANA, ALENA STRIZEK, BECCA S. FELDMAN, Haifa, Israel; Tel Aviv, Israel; Sydney, Australia; Indianapolis, IN; Rishon Le Zion, Israel; Raanana, Israel

Background: The Diabetes Conversation Map™ Program serves Clalit Health Services members with type 2 diabetes Mellitus (T2DM) for over 1 year, administered by over 400 trained certified nurses. A formal evaluation of the programmatic factors of Map™ has not yet been performed.

Methods: This was a retrospective cohort study of 5,597 participants with T2DM who enrolled in the Map™ program between 1.1.2010 and 4.1.2015. Using Cox and Poisson regression models and testing for hierarchical regression with random effects, we assessed the association between program factors (nurse instructor, enrollment year, and number of Map™ sessions attended), and outcomes (laboratory test results, adherence, and healthcare utilization) during a 12 month follow-up period.

Results: Introducing the random effect of nurses who conducted the session resulted in improved competence and knowledge regarding the utility of intervention, average hemoglobin A1c dropped to 9.7% from 11.5%, and 34 (58%) patients had an absolute decrease in their HbA1c from pre-intervention period. HbA1c dropped below 9% in 12 patients (20%). The intervention is currently ongoing.

Supported By: Eli Lilly and Company

Digging Deep into Diabetes—Barriers to Achieving Glycemic Control in Diabetic Patients in a Resident-Run Clinic

SARA HAWATMEH, MAGGIE MEIER, OSMAN QAIYUM, MUHAMMAD FARHAN ASGHAR, AMIR TALEBAN, HARINDERJEE Kaur, RAMZA HAGUE, RAJAT SHAILLY, HAMEEDE KAWSAR, St. Louis, MO; Chesterfield, MO

Introduction: Diabetes mellitus (DM) affects over 29 million Americans with an estimated annual cost of $245 billion. Diabetes in patients with multiple comorbidities, financial, and/or social hardships pose challenges to achieve target hemoglobin A1c (HbA1c). We investigated the barriers to achieve the HbA1c goal in patients in a federally funded resident-run clinic.

Methods: Among diabetic patients in our clinic, 29% had a HbA1c >9.0 in 2016. We reviewed these patients’ medical records, and interviewed them to identify the barriers in achieving HbA1c <9.0. Interviews were used to assess their knowledge about diabetes, perceived self-efficacy of disease management, confidence level regarding treatment plan, and the patient’s declaration of barriers of diabetic management. Then, we conducted an intervention to include regular telephone follow-up and clinic visits to ensure adequate supplies, medication refills, and diet and medication compliance. We have also engaged social service workers to address issues with transportation, medication costs and insurance coverage.

Results: A total of 87 patients with HbA1c >9.0 qualified for the study, 94% were African American with female predominance (55%). Average age was 52.2 years and average BMI was 33.32 kg/m². Average HbA1c was 17.5%. We were able to reach 59 patients to interview: Of those reached, 98% knew they had DM, 83% knew about HbA1c, but only 32% knew their last HbA1c. Major obstacles to achieve HbA1c goal were noncompliance with diabetic diet (29%), inability to afford medications (22%), inadequate medication refills (25%) and forgetting to take medication (20%). After 3 months of intervention, average hemoglobin A1c dropped to 9.7% from 11.5%, and 34 (58%) patients had an absolute decrease in their HbA1c from pre-intervention period. HbA1c dropped below 9% in 12 patients (20%). The intervention is currently ongoing.

Supported By: Novo Nordisk

Novel Insulins and Fixed-Ratio Combinations—Effect of Case-Based Online Education on Physician Knowledge and Competence

ATHENA PHILIS-TSIMIKAS, GILLIAN A. GRIFFITH, JOACHIM TRIER, San Diego, CA; Edinburgh, United Kingdom; New York, NY

Purpose: To determine if case-based online medical education for diabetologists/endocrinologists (diabs/endos) and primary care physicians (PCPs) can improve knowledge and competence regarding the role of novel insulins and their fixed-ratio combinations (FRCs) in treatment strategies for patients with T2DM.

Methods: This educational initiative incorporates branching logic to individualize clinical problem-based learning via case-based instruction. Each of two patient cases included both clinical decision questions (CDQs) and knowledge assessment questions (KAQs). Tailored feedback and clinical consequences were provided for CDQs and percent of correct answers on second attempt after feedback recorded. Pre- and post-multiple choice were compared for the KAQs and a paired 2-tailed t-test was used for statistical analysis. Effect sizes were calculated with Cohen’s d.

The activity launched March 24, 2017, data were collected until April 24, 2017.

Results: Participation in the activity significantly advanced knowledge/competence of diabs/endos (n=115) and PCPs (n=568). 43%-91% of diabs/endos and 27%-75% of PCPs answered a CDQ correctly on the first attempt while 16%-47% of diabs/endos and 19%-60% of PCPs improved their clinical decisions after receiving tailored feedback with an overall large effect size of 1.88 (diabs/endos) and 1.87 (PCPs). Correct responses of KAQs were 2%-13% higher for diabs/endos and 5%-28% for PCPs after activity completion with an overall small effect size of 0.085 (diabs/endos) and 0.108 (PCPs).

Conclusions: Participation in this innovative, case-based CME activity resulted in improved competence and knowledge regarding the utility of novel insulins and their FRCs for patients with T2DM. Despite notable improvement, both diabs/endos and PCPs would benefit from additional education on the optimal integration of these novel insulin formulations into treatment regimens for their patients with T2DM.

Supported By: Novo Nordisk
Combining Inulin and Incretins in T2DM Management—Effect of Online Education on Physician Knowledge and Competence

JOACHIM TRIER, ROBERT F. MCCRATHY, STEPHEN COLAGIURI, New York, NY, Camperdown, Australia

Purpose: To determine if online medical education for diabetologists/endo-crinologists (diabs/endos) and primary care physicians (PCPs) can improve knowledge regarding treatment options for intensification of insulin in patients with T2DM, the rationale, clinical evidence, and benefits of novel basal insulin/GLP-1 receptor agonist (GLP-1 RA) fixed-ratio combinations (FRCs) and competence related to the practical aspects of initiating and titrating such FRCs.

Methods: The educational activity consisted of a 30-min online video panel discussion with synchronized slides. Educational effect was assessed with a repeated pairs pre- and post-assessment study with a 3-item, multiple-choice, knowledge and competence questionnaire and a confidence assessment for all questions, each participant acts as his/her own control. A χ²-answered test assessed statistical significance at the P < .05 level. The activity launched November 30, 2016; data were collected until January 23, 2017.

Results: Participation in the activity significantly (p < .05) improved knowledge and competence of diabs/endos (average from 28% to 55%, n=99) and PCPs (average from 24% to 52%, n=129) with respect to initiating novel insulin FRCs in patients with T2DM, in particular understanding the benefits of novel short- and long-acting FRCs, how a basal insulin/GLP-1 RA FRC is effective in HbA1c reduction whilst offering better tolerability compared to monotherapy. Confidence levels in starting and titrating such FRCs in patients with T2DM uncontrolled on basal insulin also improved (57% in diabs/endos, 67% in PCPs).

Conclusions: Participation in an online video panel discussion improved knowledge, competence and confidence regarding the clinical benefits and use of novel insulin FRCs in appropriate patients with T2DM. Further education is warranted on these topics and for selecting the correct titration scheme for transitioning patients with uncontrolled T2DM receiving basal insulin.

Supported By: Novo Nordisk

Ocho Pasos a la Buena Salud (Eight Steps to Better Health)—A Diabetes Education Program for Low-Literacy Latinos With or at Risk for Type 2 Diabetes (T2D)

JAMIE CREASON, MARY M. CONNELLY, CEARA AXELROD, WENDY C. BEVIER, JENIFER SWARTZENTRUBER, DAVID KERR, Santa Barbara, CA

Ocho Pasos (Eight Steps) is a culturally relevant diabetes education program designed for low-income, low literacy Latino adults. The main focus is to improve health for those challenged with multiple socio-economic barriers. Classes are taught in Spanish over 8 weeks in a community setting. Diabetes-friendly diet modifications, compatible with culturally appropriate food traditions (e.g., reducing Tortilla consumption), are emphasized. Education, covering T2D risk factors, self-monitoring, stress management, and physical activity, is delivered using images, food models, and visual and tactile teaching aids. HbA1c (A1C Now™ PTS Diagnostics, Indianapolis, IN), BMI, and waist circumference (WC), are measured at first and last classes. Between July 2015-December 2017, 478 adults were enrolled with complete pre- and post-class data available for 127 (77% women). Of these 38 had HbA1c ≥ 6.5%, 43 between 5.7-6.4%, and 46 < 5.7% at entry. For those with initial HbA1c > 6.5%, this decreased 0.74% (p<0.01). For those between 5.7-6.4%, HbA1c fell 0.13% vs. entry (p=0.05). BMI decreased from 30.1±4.2 to 30.0±6.1 kg/m2 (p=0.01) and WC from 39.5±5.9 to 38.8±5.1 in, (p=0.01).

Daily average Tortilla consumption decreased from 5.1±2.7 to 2.4±2.7 tortillas/day (p<0.01). Participants who decreased daily tortilla consumption showed a significant reduction in their HbA1c (p<0.05), and 52% also reported more exercise after attending. Participants with HbA1c ≥ 6.5% had the greatest class attendance; 95% attended ≥5 classes.

Ocho Pasos a la Buena Salud is an effective diabetes education program for Latinos who face serious health care challenges for achieving optimal glycemic control or prevention of T2D.

Supported By: California Endowment; Crawford Idema Family Foundation; Yardi Foundation; Birdwell Family Trust

More Patients with Optimal Glycemic Control after Participation in a CSII-Specific Education Program (INPUT)—Results from a Randomized Controlled Study

BERNHARD KULZER, DOMINIC EHRRMANN, MELANIE SCHIPFER, BERNHARD LIPPMANN-GRÖSE, THOMAS HAAK, NÖRBERT HERMANN, Bad Mergentheim, Germany

Despite the technological advances of CSII-therapy, many patients with CSII-therapy do not achieve optimal glycemic control. We developed an education program for CSII-therapy (INPUT) and evaluated its efficacy in a randomized controlled trial with a six-month follow-up. INPUT addresses the specific knowledge and skills to effectively handle CSII-therapy as well as possible psychological barriers. We analyzed whether participation in the INPUT program increased the number of patients with optimal glycemic control (HbA1c < 7.5%). 254 patients with CSII-therapy were randomized to either receive the INPUT education program or treatment-as-usual and were assessed at follow-up. All patients were already performing CSII-therapy for 8.7 ± 6.8 years, with a mean diabetes duration of 23.1 ± 12.6 years. HbA1c at baseline was 8.3 ± 0.9%. Optimal glycemic control at baseline was achieved by 13% in the INPUT group and 20% in the control group. Logistic regression with group as independent factor controlling for optimal glycemic control at baseline was performed. Dependent variable was optimal glycemic control at the six-month follow-up. Group was a significant predictor with INPUT patients having a 2-fold higher chance to achieve optimal glycemic control (OR = 1.98; 95% CI 1.04-3.78; p = 0.037) compared to patients in the control group. At follow-up, 27% of the INPUT group had achieved optimal glycemic control while only 18% in the control group. In this study, patients performed CSII-therapy for almost 10 years without achieving optimal glycemic control. After participation in INPUT, patient more often achieved optimal glycemic control compared to a treatment-as-usual control group. Thus, the INPUT education program was effective in improving glycemic control in patients with long-standing diabetes. Considering the higher costs of CSII-therapy, this beneficial effect of the education program has health-economic implications.

Supported By: Berlin-Chemie AG

Marketing and Communication Strategies to Increase Enrollment in National Diabetes Prevention Program—Implications for Evaluating of Technical Assistance

YVONNE MENSIA-WIJUMOT, SHELLY-ANN BOWEN, SHARANYA THUMMALA-PALLY, MONICA D. MURPHY, GIA E. RUTLIDGE, Atlanta, GA

Under a 4-year federally funded program, states (18) and large cities (4) are implementing approaches to scale and sustain the National Diabetes Prevention Program (National DPP) as a structured, evidence-based, year-long lifestyle change program to prevent or delay onset of type 2 diabetes in people with prediabetes or at risk of developing the disease. This study examines grantee utilization of health marketing strategies to increase enrollment in the National DPP, targeting both general and high-risk populations experiencing health or socioeconomic disparities, and the technical assistance (TA) provided to grantees to implement and evaluate their marketing strategies. Analysis of Yr2 annual performance measure reports indicated that 2.2 million people were reached through traditional (print, television, radio, etc.) and social media (Facebook, Wiggio, YouTube, etc.). Over 17,000 new participants enrolled in National DPP with more than 2,000 from high-risk populations. Qualitative analysis of grantee evaluation reports and TA records revealed barriers and facilitators, such as unavailability of National DPP programs and consistent provider referrals, respectively. TA to assist grantees with program activity and performance measure alignment helped grantees improve data collection and reporting. However, gaps continue to exist between activities implemented and data reported. Recommendations for future TA include 1.) providing early guidance on marketing strategies, 2.) assisting grantees with outcome assessment, and 3.) demonstrating linkages between marketing efforts and performance measures.
**673-P**

Novel Approach to Sarcopenia in Diabetic Patients Treated with GLP-1 Receptor Agonists (GLP-1RA)

SHIN IKEJIMA, SEIYA KONDO, TAKENORI SAKAI, HISANORI TANAI, TOMOHI TAKAHASHI, JUNKO UMEZU, MAMI IKEWA, MAYA INOUE, HARUMI NISHIHARA, KAZUYA MURATA, AZAN HIROHITO, ODA, JAPAN; Utsunomiya, Japan; Yawatahama, Japan; Yurino, Japan; Tokyo, Japan, Minako, Japan; Tsukuba, Japan; Ichihara, Japan; Ise, Japan

**Background:** It is expected that GLP-1 Receptor Agonists (GLP-1RA) have not only glucose lowering effect but also weight loss and protection of diabetic kidney disease. On the other hand, sarcopenia and frailty is becoming important, because elderly diabetic patients increase in Japan. In the present study, we report about falling risk, dietary surveys and exercise therapy of diabetic patients treated with GLP-1RA.

**Methods:** The questionnaire was tested in type 2 diabetic outpatients treated with GLP-1RA at our hospital (mean age 65.7 years). The control group was the diabetic outpatient treated without GLP-1RA in nearly the same age range (mean age 63.6 years). We measured hand grip strength and one-leg standing (OIS) time. Participants were defined as patients with a high risk of falling. If their handgrip strength was ≤30kg (male) or ≤20kg (female) and their OIS time was <20s. Especially if their OIS time was <5s, defined as patients with a severe high risk of falling. We also analyzed their dietary surveys in three days. Finally, we planned original exercise program to patients with a high risk of falling, and investigated the effect of this exercise every month.

**Results:** A total of 194 cases (male, 61%; female, 39%) were included in this study. The prevalence of patients with a high risk falling was 36.1%. In patients treated with GLP-1RA (92 cases) and without GLP-1RA (102 cases), the prevalence of patients with a high risk falling was 45.7% and 27.5%. In patient treated with GLP-1RA, the prevalence of patients with severe high risk falling was 27.5% in iraglutide group (51 cases) and was 36.6% in dulaglutide group (41 cases). Dietary surveys and the effect of exercise program are on-going.

**Conclusion:** These findings show that type 2 diabetic patients treated with GLP-1RA are high risk group of falling compared with patients treated without GLP-1RA. Therefore, in use of GLP-1RA, we should be careful of sarcopenia and frailty involves in weight loss and muscle atrophy. Exercise and diet therapy are important.

**674-P**

The Impact of Lifestyle Intervention on Stage of Change toward Healthy Eating and Development of Diabetes in Prediabetic Individuals in Precontemplation Stage

NAOKI SAKANE, SHINSUKE NIRENGI, KAGURO TAKAHASHI, AKIKO SUGANUMA, KENTARO OKAZAKI, KAZUO IZUMI, MITSUHIKO NODA, HIDESHI KUZUYA, KYOTO, Japan; NAGoya, Japan; Tokyo, Japan, Saitama, Japan

**Objective:** The aim of this study was to evaluate the stages of change toward healthier behavior by telephone-delivery intervention in prediabetic individuals.

**Research Design and Methods:** A total of 2607 participants aged 20-65 years without diagnosed diabetes were randomized to a one-year telephone-intervention intervention arm (n=1240) or a self-directed control arm (n=1367). Stages of change were assessed using a self-administered questionnaire.

**Results:** At the baseline, 5.9% were in the precontemplation stage, 50.6% were in the contemplation stage, and 25.5% were in the preparation stage toward healthy eating. At the baseline, 9.4% were in the precontemplation stage, 50.2% were in the contemplation stage, and 12.0% were in the preparation stage in the change toward adopting exercise habits. Participants who self-monitored their fat intake consistently were more likely to achieve ≥5% weight loss (Table). Our findings suggest that many persons with T2DM can achieve substantial weight loss through participation in DPP lifestyle intervention.

**Conclusion:** The intervention advanced the stages of changes toward healthy eating and might be effective for preventing diabetes even in the precontemplation stage.

**675-P**

Weight Loss among Adults with Type 2 Diabetes Participating in the Diabetes Prevention Program

DOROTA CARPENEDO, SARAH M. BROKAW, SONJA TYSK, JESSIE FERNANDES, STEVEN D. HELGERSON, TODD S. HARWELL, MONTANA DIABETES PREVENTION PROGRAM STUDY GROUP, Helena, MT, Seattle, WA

**Evidence suggests substantial weight loss may be associated with remission of T2DM.** We assessed weight loss in adults with T2DM participating in an intensive lifestyle intervention using the National Diabetes Prevention Program (DPP) curriculum. While enrollment was targeted toward adults at high-risk for T2DM, adults with T2DM who were referred by their primary care provider and received medical clearance to participate were also permitted to enroll in the DPP (N = 105). Seventy percent of these participants were female; the mean age and baseline BMI were 59.2 years (SD 8.9) and 38.7 kg/m² (SD 7.7), respectively. The mean number of core sessions and total sessions (22 total sessions) completed by participants was 12.1 (SD 3.8) and 14.5 (SD 5.5). Sixty percent of participants achieved the physical activity goal of ≥150 minutes of moderate physical activity. Forty-six percent and 28% of participants achieved ≥5% and ≥7% weight loss, respectively. Results of the multiple logistic regression models indicated that participants who self-monitored their fat intake consistently and met the physical activity goal were more likely to achieve the 7% weight loss goal and participants who self-monitored their fat intake consistently were more likely to achieve ≥5% weight loss (Table). Our findings suggest that many persons with T2DM can achieve substantial weight loss through participation in DPP lifestyle intervention.

**Table. Factors Independently Associated with Achieving Seven Percent and Five Percent Weight Loss among Participants with T2DM Enrolled in the Montana Diabetes Prevention Program, 2008-2016.**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Achieved 7% weight loss at 4 months</th>
<th>Achieved 5% weight loss at 4 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>60+</td>
<td>0.82 (0.27-2.5)</td>
<td>0.72 (0.27-2.32)</td>
</tr>
<tr>
<td>36-59</td>
<td>1.0 Reference</td>
<td>1.0 Reference</td>
</tr>
</tbody>
</table>

**Sex**

<table>
<thead>
<tr>
<th></th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>95% CI</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>1.04 (0.31-3.55)</td>
<td>0.93</td>
<td>0.41 (0.13-1.33)</td>
</tr>
<tr>
<td>Male</td>
<td>1.0 Reference</td>
<td>1.0 Reference</td>
<td></td>
</tr>
</tbody>
</table>

**Baseline BMI (kg/m²)**

<table>
<thead>
<tr>
<th></th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>25.0-29.9</td>
<td>1.41 (0.29-9.33)</td>
<td>0.69</td>
</tr>
<tr>
<td>30.0-34.9</td>
<td>1.04 (0.28-3.82)</td>
<td>0.85</td>
</tr>
<tr>
<td>35+</td>
<td>1.0 Reference</td>
<td>1.0 Reference</td>
</tr>
</tbody>
</table>

**Core self-monitored fat (weeks)**

<table>
<thead>
<tr>
<th></th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>14-16</td>
<td>5.67 (1.67-27.55)</td>
<td>0.02</td>
</tr>
<tr>
<td>7-13</td>
<td>2.07 (0.44-9.74)</td>
<td>0.81</td>
</tr>
<tr>
<td>0-6</td>
<td>1.0 Reference</td>
<td>1.0 Reference</td>
</tr>
</tbody>
</table>

**Physical activity goal**

<table>
<thead>
<tr>
<th></th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Met</td>
<td>2.92 (0.86-9.88)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

**Unmet**

<table>
<thead>
<tr>
<th></th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 Reference</td>
<td>1.0 Reference</td>
<td>1.0 Reference</td>
</tr>
</tbody>
</table>

*95% CI-Ninety-five percent confidence interval. Supported By: Centers for Disease Control and Prevention

**676-P**

Weight Loss Achieved by Participants with Hypertension/Elevated Blood Pressure in a Diabetes Prevention Program

SARAH M. BROKAW, DOROTA CARPENEDO, SONJA TYSK, JESSIE FERNANDES, STEVEN D. HELGERSON, TODD S. HARWELL, MONTANA DIABETES PREVENTION PROGRAM STUDY GROUP, Helena, MT, Seattle, WA

In light of new national guidelines by the AHA/ACC that recommend lifestyle intervention as the primary mode of treatment for adults with hypertension (HTN), we assessed weight loss achieved by adults that had a HTN diagnosis and/or a measured blood pressure (BP) ≥140/90 mm Hg in an intensive lifestyle change intervention provided by lifestyle coaches using the National Diabetes Prevention Program (DPP) curriculum. From 2008-2016, 6,418 participants enrolled in the Montana DPP, and 95% (n=3,542) had HTN/BP on enrollment. Participants with HTN/BP were significantly older, weighed more at baseline, had greater fasting glucose, and attended more sessions than did other participants (Table). After the 16-week core sessions four months,
participants in both groups achieved significant weight loss. Results from the logistic regression model indicated that the factors independently associated with achieving ≥7% weight loss were being female [AOR 0.57, 95% 0.44-0.74], having low prediabetes risk score of 3-8 [AOR 0.60, 95% 0.40-0.89], meeting the physical activity goal [AOR 1.46, 95% 1.17-1.82], and self-monitoring fat for 7-13 weeks [AOR 5.36, 95% 4.10-7.81] and 14-16 weeks [AOR 12.81, 95% 8.87-18.49]. These data suggest, the DPP is likely an effective method to support adults with HTN/BP in making recommended lifestyle changes and decreasing an important blood pressure risk.

**Table.** Participant Baseline Characteristics and Outcomes During the 16-Week Core (Four Months), by Hypertension/ BP Status, Montana DPP, 2008-2016.

<table>
<thead>
<tr>
<th>Hypertension/ BP ≥140/90 (N = 4,352)</th>
<th>No Hypertension/ BP &lt;140/90 (N = 2,828)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Age (Years)</td>
<td>55.8 (11.6)</td>
</tr>
<tr>
<td>Sex (Female)</td>
<td>79.1 (2,836)</td>
</tr>
<tr>
<td>Prediabetes risk score (low 3-8)</td>
<td>79.1 (1,015)</td>
</tr>
<tr>
<td>Blood glucose (mg/dL)</td>
<td>101.4 (13.7)</td>
</tr>
<tr>
<td>Self-monitored fat intake 14-16 weeks</td>
<td>20.8 (1,015)</td>
</tr>
<tr>
<td>Achieved ≥7.5% weight loss</td>
<td>47.4 (1,701)</td>
</tr>
<tr>
<td>Achieved ≥7% weight loss goal</td>
<td>31.7 (1,138)</td>
</tr>
<tr>
<td>Baseline BMI (kg/m2)</td>
<td>37.1 (7.3)</td>
</tr>
<tr>
<td>Baseline fasting blood glucose (mg/dL)</td>
<td>35.2 (7.0)</td>
</tr>
<tr>
<td>Sessions attended</td>
<td>15.0 (6.1)</td>
</tr>
<tr>
<td>Weight change (kg)</td>
<td>5.1 (5.3)</td>
</tr>
</tbody>
</table>

*P≤0.05.

Supported By: Centers for Disease Control and Prevention

**Free Diabetes Smartphone Apps—Downloads and Rankings 2016 vs. 2017**

**Purpose:** Do the frequency of downloads of free diabetes smartphone apps change from year to year?

**Methods:** Using Google playstore, we found the most popular apps in 2017. For 2016 apps, we used our 2016 data¹ from the Google playstore. The 11 most popular free apps in 2016 and 2017 were compared.

**Results:** The change in app ranking were associated with “pay for premium features (PFP)” in 2017. The app, mySugr remains no. 1 in terms of number of downloads, due to fewest changes in PPF. Diabetes M went from no. 5 in 2016 to no. 8 in 2017, due to PFP. Glucose Buddy remained at no. 4 in the two years. Blood Glucose Tracker went from 2 to 11 in two years due to high cost PPF. Of the most popular apps in 2017, Diabetes Plus is only free on android. In 2016, only 2 are for children.Caregiver with Lenny and mySugr Junior. As of 2017, mySugr Junior no longer exists. None of the 2017 or 2016 apps have glycemic index. All apps in 2017 require email login. 4/11 apps record height and weight in 2017. 3/11 apps do not record blood pressure in 2017. 5/8 apps were journal based vs. 12/12 apps in 2017.

**Conclusions:** The popularity of apps change greatly in 24 months. Patients and MDs have a common goal in seeking useful mobile apps for diabetes self-management.

**Do Free Smartphone Apps Have Features of the Diabetes Self-Management/Education Support Guidelines?**

**Purpose:** Assessing free diabetes smartphone apps in 2016 and 2017 for popularity and features of the Diabetes Self Management/Education Guidelines (DSME) from the ADA.

**Methods:** Google analytics were used to evaluate the 11 most popular apps for 2016 and 2017. The apps were then assessed with the ADA’s DSME guidelines. The 2016 app ranking was taken from our unpublished data.²

**Results:** While 8/11 had HbA1c in 2016, this category improves to 100% in 2017. In 2016 vs. 2017: 7/11 vs. 10/11 used calorie counting. For triglycerides and lipids, both in 2016 and 2017, only one app features this category. For psychological mood, there were two apps with this feature in 2016 but only one in 2017. Goal setting in 2016 vs. 2017: 4 vs. 5.

**Conclusions:** The apps from 2017 are greatly improved over 2016. All except one app show cal/carbs, HbA1c/BPS, medical diary/log. However there is still room for improvement for the categories of Triglycerides/lipids, Psychological mood, BMI and Goal setting. We, as physicians, look forward to more robust free apps for diabetic patients.


**The Alarming Inadequacy of Adult Vaccination—Vaccination Rates in Diabetic Patients**

**Purpose:** To determine the adult vaccination rates (VR) in diabetic patients who are in routine follow-up in our outpatient diabetes clinic.

**Methods:** 846 DM patients that were included in the study, were selected by simple random sampling and their demographic data were recorded. Patients were asked if they were vaccinated for influenza in last 1 year, tetanus in last 10 years, hepatitis B and pneumococcus. In the 846 patients, 11,2(1-50). VR were 17.6% (n=149) for influenza, 18.6% (n=157) for tetanus, 8.6% (n=73) for hepatitis B and 5.4% (n=46) for pneumococcus.

**Conclusion:** Do Free Smartphone Apps Have Features of the Diabetes Self-Management/Education Support Guidelines?

GÜNEŞ FEYZİOĞLU, ASLI KARSLI, AYTEKİN OĞUZ, İstanbul, Turkey

**Aim:** DM is a disease that causes immune incompetence due to various reasons. Therefore, the risk of infectious disease and the risk of complications, morbidity and mortality related to infectious disease in diabetic patients are increased compared to healthy adults. Patients with DM are advised to get vaccinated for influenza once every year, tetanus every 10 years, hepatitis B if they did not complete their routine vaccinations and pneumococuss for once. Researches reveal the lack of adult vaccination awareness, even in high risk group of patients. This study is designed to determine the adult vaccination rates (VR) in diabetic patients who are in routine follow-up in our outpatient diabetes clinic.

**Methods:** Simple random sampling and their demographic data were recorded. Patients were asked if they were vaccinated for influenza in last year, tetanus in last 10 years, hepatitis B and pneumococcus. In the 846 DM patients that were included in the study, the average age was 58.7 (32-88) and the average years with diabetes was 11.2(1-50). VR were 17.6% (n=149) for influenza, 18.6% (n=157) for tetanus, 8.6% (n=73) for hepatitis B and 5.4% (n=46) for pneumococcus.

**Conclusion:** The popularity of apps change greatly in 24 months. Patients and MDs have a common goal in seeking useful mobile apps for diabetes self-management.
The Influence of Outpatients’ Wait Times and Health Care Professionals’ Communication Behaviors on Treatment Satisfaction and the Intention to Drop Out

SHIJI SATO, TAKAHIRU TSUKAI, CHIE OSHIRO, AYAE KUDARA, AKEMI INAGAKI, MASAKI KÔNDO, SHIN TADENKAWA, YOSHIRO KATO, HIDEKI KAMIYA, JIRO NAKAMURA, NAPPU JAPAO, NAGAKI, Japan

We studied influences of perceptions of patients’ wait times and communication behaviors of healthcare professionals on treatment satisfaction and the intention to drop out in diabetes outpatients. A questionnaire was sent to 888 outpatients with diabetes or impaired glucose tolerance who visited our clinic in April 2016. We also measured time spent in clinics. Totally, 759 patients responded to the questionnaire; 717 valid responses were obtained for statistical analyses. In the group with the intention to drop out, many replied that they felt that “the wait time from physical examination to accounting” was long; this association was significant (P = 0.009, χ² test). Time spent in clinics was also significantly associated with the “perception of wait time (total).” Communication behaviors of healthcare professionals were also significantly associated with the presence of the intention to drop out. Median scores of the first factor of the Diabetes Treatment Satisfaction Questionnaire (DTSQ) were lower in those who intended to drop out than in those who did not (52 vs. 632 patients); the DTSQ first factor score was significantly associated with the presence of intention to drop out (P < 0.001, Mann–Whitney U test). Receiver operating characteristic curve analysis revealed the DTSG score as a significant predictor of the presence of intention to drop out (area under the curve = 0.746, P < 0.001), with an optimal cut-off of 22.5 (sensitivity 70.6%, specificity 87.3%). The findings of this study suggest that improved treatment satisfaction may reduce incidences of drop out. Thus, improved wait times and better communication behavior from healthcare professionals may improve patient satisfaction and reduce the intention to drop out and possibly the dropout rate.

Diabetes Self-Management Education (DSME) and Diabetes Preventive Care Practices among People With and Without Vision Impairment

SWATHI SEKAR, ROBERT B. GERZOFF, JINAN B. SAADDINE, MAGON M. SAUNDERS, Atlanta, GA

Objective: To examine whether participating in Diabetes Self-Management Education (DSME) was associated with increased diabetes preventive care practices among those with and without self-reported vision impairment (VI). Background: Over 30 million people in the United States have diagnosed diabetes. DSME is a vital component of care, facilitating the knowledge and skills needed to improve self-care for diabetes. Those with VI are more likely to have diabetes than those without, highlighting a need to examine DSME participation and preventive care practices among those with and without VI.

Methods: We used data from the 2015 Behavioral Risk Factor Surveillance System (BRFSS), a large ongoing landline and cellular telephone based survey. The question “Have you ever taken a course or class in how to manage your diabetes yourself?” was asked in 37 states plus the District of Columbia and Guam. In a logistic regression, we examined if the association between DSME and preventive care practices was significantly modified by VI status.

Results: Regardless of VI status, respondents with diabetes who participated in DSME had a greater predicted probability of engaging in each preventive care practice than those who did not. Compared to respondents with VI who did not participate in DSME, those with VI who participated in DSME had a significantly greater predicted probability of having administered a daily glucose check (83.7% vs. 59.3%) and having had an annual visit to a health care professional for their diabetes (95.3% vs. 82.1%).

Conclusions: Participants with VI who received DSME have increased predicted probability of engaging in certain self-care practices compared to those with VI who did not receive DSME. This highlights the importance of people with diabetes and VI acquiring the appropriate tools to positively affect their own health.
HCP and Patient Perspectives on Basal Insulin Titration

CHIMA UZOIGWE-SMITH, MARGARITA LEVIN, DOUGLAS B. PFAFF, MICHELLE MOCARSKI, CAROL M. HAMERSKY, WILLIAM POLONSKY, Plainsboro, NJ, New York, NY, Del Mar, CA

Little is known about the discussion regarding titration at the time basal insulin is initiated for people with type 2 diabetes (T2D) and about how titration occurs in the real world. This qualitative study investigated attitudes and practices of health care professionals (HCPs) and patients associated with basal insulin titration. Twelve virtual focus groups, comprising 23 HCPs (8 endocrinologists, 15 primary care physicians) and 22 adult patients with T2DM whose length of time since starting basal insulin was ≤ 4 years, were recruited from panels across from the U.S. from June to August 2017. Fifteen of 23 HCPs (65%) reported that they typically discussed titration at the time basal insulin was first prescribed. Twelve of 23 (52%) discussed target blood glucose (BG) ranges in initial conversations. Thirteen of 23 (57%) said most of their patients did not completely understand elements of the titration discussion. Of 16 HCPs who discussed what they do when their patients appear overwhelmed by or do not comprehend treatment instructions, 9 would start most of their patients on HCP-guided titration, 5 would delay titration and 2 would encourage self-titration without delay. HCPs on average reported 43% of their adult T2DM patients reached their A1c target within 6 months; they also reported 40% of their self-titrating patients ever reached their A1c target. Seventeen of 22 patients (77%) began titration when basal insulin was prescribed, and recalled injection and dose adjustment instruction from initial conversations. Twelve of 22 (55%) felt they were provided insufficient context on expectations around increasing insulin and/or how long titration could take. Four patients said they linked dose increases to personal failure. Eleven of 22 patients identified as self-titraters. Of 16 patients aware of their A1c or BG targets, 5 (31%) achieved dose increases to personal failure. Eleven of 22 patients identified as self-titraters. Of 16 patients aware of their A1c or BG targets, 5 (31%) achieved dose increases to personal failure. Four patients said they linked dose increases to personal failure. Eleven of 22 patients identified as self-titraters. Of 16 patients aware of their A1c or BG targets, 5 (31%) achieved dose increases to personal failure. Four patients said they linked dose increases to personal failure. Eleven of 22 patients identified as self-titraters.
problems perception related to anxiety/depression from 63.2% to 26% (p<0.001). This non-pharmacological therapeutic approach focused on DSME improved HbA1c. Our findings suggest the role of DSME in this population beyond the traditional physical component impact, since it favors the fulfillment of multiple interrelated objectives through different mechanisms, generating a diversity of positive results, including HRQoL.

688-P
Virtual Simulation Improves Clinical Decision-Making in Managing Type 2 Diabetes
AMY LARKIN, KELLY L. HANLEY, MARTIN WARTERS, GWEN S. LITTMAN, New York, NY; Durham, NC
This study was conducted to determine if online, virtual patient simulation (VPS)-based continuing medical education (CME) intervention that engages clinicians in a practical learning experience could improve performance of diabetologists/endocrinologists (D/Es) and primary care physicians (PCPs) in the management of T2D and sleep problems. The CME VPS intervention comprised one patient presenting at 2 different points. The VPS platform allows learners to order lab tests, make diagnoses, and prescribe treatments in a manner matching the scope and depth of actual practice. Learners’ choices were analyzed using a sophisticated decision engine. Tailored clinical guidance (CG), based on current evidence and expert recommendations, was provided following each decision. Learners were given the opportunity to modify their decisions after receiving CG. Decisions were collected post-CG and compared with each user’s baseline (pre-CG) decisions using a 2-tailed paired t-test to determine P-values. Through November 2017, significant improvements were documented among participating learners after clinical guidance (D/Es n=19; PCPs n=39):

- • Diagnosis of uncontrolled T2D: 40% absolute improvement among PCPs (3% pre-CG vs. 43% post-CG; P<0.001) and 26% improvement among D/Es (0% pre-CG vs. 26% post-CG; P<0.001).
- • Diagnosis of insomnia: 31% absolute improvement among PCPs (28% pre-CG vs. 58% post-CG; P=0.001) and 53% improvement among D/Es (11% pre-CG vs. 47% post-CG; P<0.001).
- • Insomnia treatment: 56% absolute improvement among PCPs (10% pre-CG vs. 68% post-CG; P<0.001) and 42% improvement among D/Es (11% pre-CG vs. 53% post-CG; P<0.001).
- • Intensification of T2D treatment: 36% absolute improvement among PCPs (28% pre-CG vs. 64% post-CG; P<0.001) and 35% improvement among D/Es (29% pre-CG vs. 65% post-CG; P<0.013).

This study demonstrates that VPS that immerses and engages the clinical learners in an authentic and practical learning experience can improve evidence-based clinical decisions related to the management of T2D.

Supported By: Merck & Co. Inc.

689-P
The Impact of Restricted Gestational Weight Gain on Fetal Growth during Dietary Treatment in Women with Gestational Diabetes Mellitus
LISE KURTH-NIELSEN, SIDSE NIBGAARD, HELLE RONNEBY, ANNA L. SECHER, ANN TABOR, H. DAVID MCINTYRE, PETER DAMM, ELISABETH R. MATHIESEN, Copenhagen, Denmark; South Brisbane, Australia
Aim: To investigate the impact of maternal gestational weight gain during dietary treatment (GWG-diet) on fetal growth in pregnancies complicated by gestational diabetes (GDM).

Material and Methods: A retrospective cohort study of 382 consecutive women diagnosed with GDM <34 weeks and live singleton births in our center in 2011-2017. The women were stratified according to restricted (52%), appropriate (17%) and excessive (31%) weekly GWG-diet (Institute of Medicine guidelines) to estimate compliance to a calorie-restricted diabetes diet (1700 kcal daily). Insulin therapy was initiated according to local clinical guidelines.

Results: Glucose tolerance, HbA1c, GWG before dietary treatment (GWG-before) and fetal abdominal circumference standard deviation (SD) score were comparable across the three GWG-diet groups at referral at 27±3 weeks. The women were followed for 10±5 weeks, 54% received insulin therapy and the average GWG-diet in the three groups was 0 kg, 3 kg and 5 kg, respectively. Women with excessive weekly GWG-diet, also had increasing HbA1c (p=0.001) during dietary treatment and infants with a birth weight SD-score of 0.59±1.6, while women with restricted weekly GWG-diet also had decreasing HbA1c (p<0.001) during dietary treatment, and infants with a birth weight SD-score of 0.15±1.1, without intrauterine growth restriction. Excessive GWG-diet and late pregnancy HbA1c were predictors of infant birth weight SD-score (p<0.001) after correction for parity, uptake area, pre-pregnancy BMI and insulin therapy.

Conclusion: Restricted GWG-diet was associated with more appropriate fetal growth in women with GDM. GWG-diet and late pregnancy HbA1c were modifiable clinical predictors of infant birth weight SD-score.

690-P
Evaluating the Effect That Diabetes Education Has on Acute-Care Nurses’ Knowledge Level
JACKIE KUCHLA, Sioux City, IA
Although there are published inpatient diabetes guidelines, successful implementation is often met with resistance and fear of complications in treated patients. This is often due to a lack of knowledge among healthcare providers and nurses (RN), which increases the risk of complications, dysglycemia, length of stay and readmissions. Diabetes affects every hospitalization and healthcare organizations need to provide all RNs with the education to reduce the effects of uncontrolled or undiagnosed diabetes. This project developed a 25-question, multiple choice test to evaluate acute-care RNs knowledge on inpatient diabetes management and was evaluated to determine the reliability and validity of the test. Validity was verified by a certified nurse leader with advanced diabetes management to ensure the questions were within a registered nurses scope of practice and an endocrinologist verified comprehensive inclusion of published inpatient diabetes guidelines across the continuum. The questionnaire was completed by 13 RNs and included a focus on pathophysiology of type 1 and type 2 diabetes, noninsulin agents, insulin, acute complications, nutrition, and sick day management. A paired t-test statistical analysis was conducted to determine the reliability of the questionnaire post-administration of diabetes education to the same group of RNs. The comparison showed an improvement in the overall diabetes knowledge level with a mean score of 79.7%, SD=3.76; compared to pre-test mean score of 77.38%, SD=14.86 and t=-3.524, p=0.004. Additional variables evaluated through a two way ANOVA (F[2, 10], F=0.31, P=0.428) showed no significant effect were the years of experience or level of nursing degree on the overall scores. In order to further strengthen the reliability of the questionnaire, the project should be repeated throughout the organization including all inpatient nursing departments. Additional variables that should be evaluated for effect include nursing unit and type of experience.

691-P
Durability of Glycemic Control in a Diabetes Education Insurer-Based Intervention in Primary Care
MARGARET ZUPA, VINCENT C. ARENA, MARGARET B. THEARLE, PATRICIA A. JOHNSON, LINDA M. SIMINERIO, Pittsburgh, PA
Background: Models that address the needs of patients with diabetes mellitus (DM) in primary care (PC) are needed, as health systems move to value-based care. To support DM patients at high risk, an insurer-based program that paired nurse practice care managers (PCMs) with certified diabetes educators (CDE) was designed to improve outcomes for DM patients with complex needs.

Objective: To assess the durability of glycemic improvement after diabetes self-management education and support (DSMES) intervention within a model that relies on a PCM to identify, refer, and provide ongoing support to complex patients who received a CDE intervention in PC.

Methods: 2 CDEs, serving rural and urban areas, were introduced as team members into PC practices. CDEs provided DM training to PCMs who then proactively identified and referred patients under clear criteria (DM related ER visits, hospitalizations, HbA1c>9, reported barriers to care) for DSMES in collaboration with PC provider and PCM. Post CDE intervention, the PCM was available for follow-up and ongoing support. HbA1c was monitored every 3 months after intervention and compared to baseline value to assess durability of improvement in glycemic control.

Results: Of 222 patients referred, 108 had 6 and 80 had 12-month data for analysis. Patients were 52% female; mean age 57 (SD 13.43). Mean HbA1c decreased from 9.6 to 8.4 over 6 months and 9.2 to 8.1 over 12 months (p<0.001). Improvement in glycemic control was maintained for at least 1 year after intervention. There was no significant change in BMI over this time.

Conclusions: A model where CDEs partner with PCMs, who identify, refer, and provide ongoing support to patients post-CDE delivery of DSMES, is an effective and feasible intervention to improve and sustain DM outcomes in PC. This collaborative approach expands opportunities to meet complex needs of DM patients and can contribute to the ability of practices and health plans to provide an effective intervention with ongoing patient support.
Evidence-Based Interventions to Control Diabetes by Local Health Departments in the United States

RACHEL G. TABAK, RENEÉ G. PARKS, PEG M. ALLEN, REBEKAH R. JACOB, STEPHANIE MAZZUCA, KATHERINE STAMATAKIS, MARSHALL CHIN, ROSS BROWNSON, ST. LOUIS, MO, Chicago, IL

The nearly 3,000 local health departments (LHDs) nationwide are the frontline of public health, and are positioned to implement evidence-based interventions (EBIs) for diabetes control. This study used a national online survey to determine the prevalence and correlates of four CDC Community Guide recommended EBIs in LHDs. Among 240 LHDs, each EBI was delivered directly or with key partners by >60% (Figure 1); 96 LHDs (40%) offered all four EBIs, and 15 (7%) offered none. Diabetes prevalence in the state was positively associated with offering the Diabetes Prevention Program (OR=1.28 [95% CI: 1.02-1.62]), diabetes self-management education (OR=1.32 [95% CI: 1.04-1.67]), and identifying patients and delivering treatment (OR=1.27 [95% CI: 1.05-1.54]) (Table). Implementation of these EBIs by more LHDs can help control diabetes.

Table. Selected Associations between Local Health Department (LHD) Characteristics and Delivering (Directly and/or With Key Partners) Diabetes Evidence-Based Interventions (EBIs) (Odds Ratio [OR] [95% Confidence Interval [95% CI]])

<table>
<thead>
<tr>
<th>LHD and respondent characteristics</th>
<th>Disclosure</th>
<th>DSME</th>
<th>DPP</th>
<th>ID</th>
<th>CHW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jurisdiction population categories</td>
<td>(n=400)</td>
<td>1.08</td>
<td>1.59</td>
<td>1.01</td>
<td>1.23</td>
</tr>
<tr>
<td>Diabetic prevalence in the state</td>
<td>(n=400)</td>
<td>1.32</td>
<td>1.28</td>
<td>1.27</td>
<td>1.06</td>
</tr>
<tr>
<td>Position [executive, health director, health office commissioner, or equivalent in the “office of the director” = referent]</td>
<td>(n=400)</td>
<td>0.67</td>
<td>0.74</td>
<td>0.82</td>
<td>1.37</td>
</tr>
<tr>
<td>Age [years]</td>
<td>(n=400)</td>
<td>0.94</td>
<td>0.94</td>
<td>0.70</td>
<td>0.71</td>
</tr>
</tbody>
</table>

**Diabetes prevalence in the state** (β=0.04) is positively associated with offering the Diabetes Prevention Program (OR=1.28 [95% CI: 1.02-1.62]), diabetes self-management education (OR=1.32 [95% CI: 1.04-1.67]), and identifying patients and delivering treatment (OR=1.27 [95% CI: 1.05-1.54]) (Table). Implementation of these EBIs by more LHDs can help control diabetes.

**Diabetes self-care behaviors (DSCBs) play a significant role in control,** and can be targeted through public health programs (strongly agree/agree vs. other)

Evidence-based interventions (EBIs) for diabetes control. This study used a national online survey to determine the prevalence and correlates of four CDC Community Guide recommended EBIs in LHDs. Among 240 LHDs, each EBI was delivered directly or with key partners by >60% (Figure 1); 96 LHDs (40%) offered all four EBIs, and 15 (7%) offered none. Diabetes prevalence in the state was positively associated with offering the Diabetes Prevention Program (OR=1.28 [95% CI: 1.02-1.62]), diabetes self-management education (OR=1.32 [95% CI: 1.04-1.67]), and identifying patients and delivering treatment (OR=1.27 [95% CI: 1.05-1.54]) (Table). Implementation of these EBIs by more LHDs can help control diabetes.

Table. Selected Associations between Local Health Department (LHD) Characteristics and Delivering (Directly and/or With Key Partners) Diabetes Evidence-Based Interventions (EBIs) (Odds Ratio [OR] [95% Confidence Interval [95% CI]])

<table>
<thead>
<tr>
<th>LHD and respondent characteristics</th>
<th>Disclosure</th>
<th>DSME</th>
<th>DPP</th>
<th>ID</th>
<th>CHW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jurisdiction population categories</td>
<td>(n=400)</td>
<td>1.08</td>
<td>1.59</td>
<td>1.01</td>
<td>1.23</td>
</tr>
<tr>
<td>Diabetic prevalence in the state</td>
<td>(n=400)</td>
<td>1.32</td>
<td>1.28</td>
<td>1.27</td>
<td>1.06</td>
</tr>
<tr>
<td>Position [executive, health director, health office commissioner, or equivalent in the “office of the director” = referent]</td>
<td>(n=400)</td>
<td>0.67</td>
<td>0.74</td>
<td>0.82</td>
<td>1.37</td>
</tr>
<tr>
<td>Age [years]</td>
<td>(n=400)</td>
<td>0.94</td>
<td>0.94</td>
<td>0.70</td>
<td>0.71</td>
</tr>
</tbody>
</table>

**Diabetes prevalence in the state** (β=0.04) is positively associated with offering the Diabetes Prevention Program (OR=1.28 [95% CI: 1.02-1.62]), diabetes self-management education (OR=1.32 [95% CI: 1.04-1.67]), and identifying patients and delivering treatment (OR=1.27 [95% CI: 1.05-1.54]) (Table). Implementation of these EBIs by more LHDs can help control diabetes.**

**Diabetes self-management education with persons with diabetes delivered in community gathering places (DSME).** Diet and physical activity promotion programs with people at increased risk for type 2 diabetes such as the Diabetes Prevention Program (DPP). Diabetes management interventions identifying patients with diabetes and delivering effective treatment (ID). Community health workers to deliver diet and physical activity promotion, and weight management to groups or individuals with increased risk for type 2 diabetes (CHW).**

**Supported By: Ascensia Diabetes Care**

**Impact of Certified Diabetes Educators following Preapproved Protocols on Diabetes Self-Care Behaviors—Results of the REMEDIES 4D Trial**

KRYS M. JOHNSON, MARKKU MALMI, JR., SHIHCHEN KUO, JANICE C. ZGIBOR, Tampa, FL, Lutz, R., Aven Arbor, MI

Diabetes self-care behaviors (DSCBs) play a significant role in controlling risk factors for diabetes-related complications when practiced consistently. Our objective was to evaluate changes in DSCBs in people with type 2 diabetes from primary care practices participating in the REMEDIES 4D study. REMEDIES 4D was a clustered, randomized trial in which certified diabetes educators (CDEs) implemented standardized treatment protocols to intensify treatment for glucose, lipid or blood pressure control. Fifteen practices and their patients were randomized to the intervention (n=175) or usual care (n=85). Eligible participants had uncontrolled HbA1c, blood pressure, or LDLc. The intervention group received diabetes self-management education in addition to treatment intensification, while the usual care group participated in monthly support groups for one year. DSCBs were measured via the Summary of Diabetes Self-Care Activities scale (SDSCA). Two-sample t-tests were conducted to examine differences in adherence to recommended daily diabetes self-care behaviors between the intervention and usual care groups. The population was 49% male with a mean age of 61 years. The main results of the trial demonstrated a significant 1% decline in HbA1c in the intervention group and no significant change in the usual care group. At baseline, intervention participants tested blood glucose (BG) an average of 4.3 days compared with usual care 3.0 days (P=0.232). At follow-up, intervention participants tested BG an average of was 4.9 days, 1.3 days more frequently than the control group (P=0.004). There was no significant difference between groups for adherence to the self-care behaviors of general diet, specific diet, exercise, or foot care. These findings suggest that CDEs following standardized treatment protocols will improve adherence to recommendations for daily blood glucose testing which may enable patients to maintain better glycemic control.

**Supported By: American Diabetes Association (1-12-SAN-31 to J.C.Z.)**

**693-P**

**Impact of Certified Diabetes Educators following Preapproved Protocols on Diabetes Self-Care Behaviors—Results of the REMEDIES 4D Trial**

KRYS M. JOHNSON, MARKKU MALMI, JR., SHIHCHEN KUO, JANICE C. ZGIBOR, Tampa, FL, Lutz, R., Aven Arbor, MI

Diabetes self-care behaviors (DSCBs) play a significant role in controlling risk factors for diabetes-related complications when practiced consistently. Our objective was to evaluate changes in DSCBs in people with type 2 diabetes from primary care practices participating in the REMEDIES 4D study. REMEDIES 4D was a clustered, randomized trial in which certified diabetes educators (CDEs) implemented standardized treatment protocols to intensify treatment for glucose, lipid or blood pressure control. Fifteen practices and their patients were randomized to the intervention (n=175) or usual care (n=85). Eligible participants had uncontrolled HbA1c, blood pressure, or LDLc. The intervention group received diabetes self-management education in addition to treatment intensification, while the usual care group participated in monthly support groups for one year. DSCBs were measured via the Summary of Diabetes Self-Care Activities scale (SDSCA). Two-sample t-tests were conducted to examine differences in adherence to recommended daily diabetes self-care behaviors between the intervention and usual care groups. The population was 49% male with a mean age of 61 years. The main results of the trial demonstrated a significant 1% decline in HbA1c in the intervention group and no significant change in the usual care group. At baseline, intervention participants tested blood glucose (BG) an average of 4.3 days compared with usual care 3.0 days (P=0.232). At follow-up, intervention participants tested BG an average of was 4.9 days, 1.3 days more frequently than the control group (P=0.004). There was no significant difference between groups for adherence to the self-care behaviors of general diet, specific diet, exercise, or foot care. These findings suggest that CDEs following standardized treatment protocols will improve adherence to recommendations for daily blood glucose testing which may enable patients to maintain better glycemic control.

**Supported By: American Diabetes Association (1-12-SAN-31 to J.C.Z.)**
Assessing the Evaluability of Type 2 Diabetes Prevention and Diabetes Management Interventions Focusing on Underserved Populations

KIMBERLY D. FARRIS, TIMETHIA BONNER, GIA E. RUTLEDGE, BRYCE SMITH, Atlanta, GA

In 2013, CDC developed the State Public Health Actions to Prevent Obesity, Diabetes, and Heart Disease and Stroke, a five-year cooperative agreement which combined the efforts of four divisions to fund 50 state health departments (SHDs) to implement strategies to work through health systems and communities to prevent chronic disease and reduce complications from multiple chronic diseases. The Division of Diabetes Translation recommended several strategies to support type 2 diabetes prevention and diabetes management. The strategies focused on 1) increasing referrals to CDC-recognized lifestyle change programs operating under the National Diabetes Prevention Program (National DPP); 2) securing the program as a covered benefit for state or public employees and Medicaid beneficiaries; and 3) increasing referrals to, coverage for, and availability of diabetes self-management education and support (DSMES) programs. Quantitative analysis of SHD performance measures data shows that from baseline to year 4, there was an increase in access to and participation in DSMES and the National DPP. Qualitative analysis of SHD plans identified program accreditation, technical assistance, partnerships, reimbursement for DSMES, and flexible scheduling for patients as key facilitators for increased DSMES program utilization. SHD grantees reported reimbursement availability, practice/provider referral policies, and having standard curricula as facilitators to implementing the National DPP lifestyle change program.

DIABETES EDUCATION

Free Weight-Loss Apps and Diabetes Management for the Patient

GLORIA WU, LAURA BILLARD, YY-YY NGO, AMY DOAN, ELENA MUNRO, BRYAN LE, San Francisco, CA; Santa Barbara, CA; Irvine, CA; Davis, CA; Tampa, FL; San Diego, CA

Weight loss and obesity are concerns shared by diabetic patients and the lay public. These search terms, “weight loss,” “obesity,” generate 72M and 30M webpages, respectively. “Diabetes” as a search term generates 104M webpages. According to Google Trends, “weight loss,” “diabetes” terms are searched 7x more than “obesity.” In 2016, there were 59,000 medical health apps. It is expected that at the end of 2017, apps will reach $32 billion in revenue. Are these apps useful to our diabetic patients?

Purpose: To evaluate free weight loss droid apps in terms of the Diabetes Self-management Education and Support Guidelines.

Methods: Using Google Play to find the most downloads in free weight loss apps in 2017. Droid apps downloads are documented by Google Play whereas iPhone apps’ downloads are not available to the public. We included only those apps that emphasized weight loss. We excluded those apps with malfunctioning web on a daily basis.

Results: The majority of the apps have calorie counting. However, 4/10 are lacking in basic information about BMI; only half of the apps have a med log/diary. None include psychological moods.

Conclusions: Weight loss mobile phone app are commonly used by the general public not only diabetic patients. Most do not track fasting blood glucose, lipids and blood pressure. There is room for improvement for this growing field of health apps and diabetes.

Cardiovascular Disease (CVD) Decision Aid for Youth with Type 1 Diabetes (T1DM)—Perspectives of Health Care Providers (HCPs) with Pediatric-Onset T1DM

JODI KRALL, INGRID LIBMAN, SAMINA AFREEN, LINDA M. SIMINERIO, Pittsburgh, PA

CVD is the leading cause of premature death in people with T1DM, yet many individuals are unaware. Strategies to engage youth in CVD prevention and lifelong disease management are needed. The purpose of this study was to gain insight from HCPs about a shared decision making (SDM) aid centered on CVD modifiable risk factors (Alc, blood pressure, BP, and cholesterol), and designed to present facts, risks/benefits, and actionable steps relevant to teenagers. Five HCPs with pediatric onset T1DM, age 27-30 years, working in a pediatric DM center, participated in multiple focus groups, to iteratively guide development of the SDM aid. Based on their experience in having T1DM and providing DM care to youth, HCPs offered perspectives on the aid in terms of value, content, delivery, and support mechanisms. Feedback was transcribed and summarized. HCPs agreed that introducing the topic of CVD to teenagers was important. Reflecting on their own experiences, HCPs regretted that the topic was not discussed during their pre-adult care conversations, which they said contributed to their unawareness of CVD prevention at the time. In terms of content, HCPs found the aid to be well suited for the intended audience, easy to understand, and not overwhelming. They thought illustrations were helpful to convey key facts and prevention messages, and voiced that even if it would be unlikely that their patients ships, instructor or coaches/participant racial concordance, holding classes in multiple locations, and including more group sessions. A panel of diabetes subject matter experts reviewed information on program design, implementation, and data collection capacity to recommend 4 programs to participate in a rigorous evaluation.
would have abnormal BP or lipids presently, educating about target values and testing intervals would be beneficial in preparation for adulthood. HCps did not anticipate that the aid would cause distress, noting it was well-balanced, informative, but not intimidating and refrained from scare tactics. HCps unanimously agreed they would use the aid with patients (and parents), and recommended applying it when reviewing lab results.

In summary, HCps endorsed using the SDM aid to guide CVD discussions with youth. Studies are ongoing to assess its impact on youth with T1DM.

---

**Training Nursing Staff to Improve Diabetes Care for Long-Term Care Facility (LTFC) Residents**

ABEgal L. HubberD, CHRISTiNAM. HenriNdez, San Antonio, TX

One out of four people age 65 and older residing in a long term care facility (LTFC) has type 2 diabetes (T2DM). Care and management of this population is a challenge for nurses and other providers. American Diabetes Association Guidelines (2017) recommend application of individualized HbA1C targets for LTFC residents, especially for those with complications in clinical and functional status.

A needs assessment in a local LTFC identified deficiencies in the provision of evidence-based T2DM care for this LTFC population. This quality improvement (QI) project strove to 1) educate nurses about these residents’ needs and 2) incorporate the use of best practice diabetes standards in the nurse practitioner’s practice by providing in-service education. Specifically, emphasis was placed on HbA1c and finger stick monitoring, eye exams, and foot care.

Results indicated that educational in-services were an effective approach to improving knowledge concerning care of complex T2DM patients. The Advanced Practice Registered Nurse (APRN) (60%) to 100%), the 3 registered nurses (63% to 87%) and 9 licensed vocational nurses (63% to 71%) increased in knowledge from baseline to the final 10 question post-test.

However, ophthalmology and podiatry referrals were not ordered routinely because of APRN staff, and organizational resistance. Per an audit of 22 patient charts, utilization of standardized orders improved routine T2DM care. There were 13 HbA1c due and 12 were ordered (92%), the one renal panel that was due was ordered, and all 5 urine to albumin creatinine ratio were ordered. In addition, the APRN has awareness to evaluate discrepancies between HbA1c results and finger stick values.

QI projects in LTFCs may be difficult to implement and sustain related to staff turnover, understaffing, high patient acuity, and organizational and provider opposition. APRNs must advocate for continual utilization of evidence-based practice guidelines for all LTFC residents.

---

**An Interdisciplinary Team Approach to Managing Diabetes in a Patient with End-Stage Renal Disease**

STEVEN M. LAMIE, JANET C. BAILLIO, STUART D. ROCKAFELLOW, MARILYN B. GIBBS, DEBRA SCHEFFERLY, Traverse City, MI

Background: Our private practice Patient-Centered Medical Home (PCMH) clinic proposed a pilot team-based program where patients would be seen between appointments by an interdisciplinary team comprised of our CDE, Clinical Pharmacist, and Care Manager with the goal of helping improve glycemic goals.

Methods: Patients age 18 or older with an A1c greater than 8.0 were identified through registry review and invited to participate. Team providers were under the supervision of the project lead physician. Number of visits was individualized for each patient. Visits centered on diabetes education, goal setting, and motivational interviewing. The project was pre-defined to have been successful if 15% of patients achieved improved control.

Results: A recruitment goal of 100 was targeted and 107 patients were identified and enrolled. One hundred and six patients completed the pilot program. Average A1c at the beginning of the study was 9.1%. A1c decreased to 8.2% at the end of pilot. 0.3% decrease. A1c ranged from 8.0 to 14.5% at pilot initiation. At the end of the pilot A1c ranged from 5.1 to 10.8%. This represents a change of -7.4 to 1.9%. Seventy patients (65%) achieved improved A1c. Forty four (41%) patients achieved an A1c less than 8.0%. An additional 26 (24%) patients have improved in A1c. Patients had an additional 7 visits on average. Average blood pressures declined by 2.7 mmHg systolic and 0.11 mmHg diastolic. Microalbumin to creatinine ratio testing increased to 95% compliance, an increase of 20%. Appropriate statin use was unchanged at 79% of patients.

Conclusions: The majority of pilot enrollees improved their diabetic control over the course of the pilot program. The pre-specified level for success was exceeded. This project demonstrates the ability of a private practice with limited resources to seek creative solutions and partnerships to improve patient care of challenging and complex patients.

Supported By: Northern Physician Organization

---

**Projecting Long-Term Diabetes Complications through a BRAVO-Based Mock Simulation for Promoting Diabetes Prevention Program (DPP)**

Hui Shao, Shuang Yang, Vivian Fonseca, Xu Ji, Liheng Shi, New Orleans, LA, Atlanta, GA

Correctly understanding consequences of diabetes is essential for motivating prediabetic patients to join the diabetes prevention program (DPP). The overall population estimates on diabetes complications may be lower than individual’s risk estimates which are subjective to their life expectancy. This study using a newly developed diabetes model aimed to project major diabetes complications, conditioning on a range of survival lengths. 2011-2016 National Health and Nutrition Examination Survey data were used to generate a nationally representative sample of newly diagnosed diabetes patients. The Building, Relating, Validating, Acting and Validating Outcomes (BRAVO) diabetes simulation model was used to project the long-term risks of diabetes complications for the NHANES sample. The cohort of simulated patients were followed up for 20/40 years, conditioning on zero mortality (i.e., mock simulation experiment) and cumulative incidence during the follow-up periods for each complication were recorded. The average age of newly diagnosed diabetes was 51.66 y. For diabetes patients who have survived for 20 years after diabetes onset, the probabilities of diabetes complications were: MI (20.4%), stroke (7.8%), congestive heart failure (CHF, 10.6%), angina (13.4%), revascularization surgery (RS, 54.4%), end-stage renal disease (ESRD, 11.7%), severe pressure sensation loss (SPLS, 56.6%), and blindness (27%). For diabetes patients who have survive for 40 years after diabetes onset, the probabilities of diabetes complications were: MI (55.8%), stroke (24.3%), CHF (46.1%), angina (34.4%), RS (85.8%), ESRD (31.7%), SPLS (68.9%), blindness (64.9%). The presentation of diabetes complications for a long survival time could help prediabetes patients better assess diabetes impact on health. The BRAVO-base decision support simulation could serve as a tool to educate prediabetes population on benefits of diabetes prevention program.

---

**You Can Build It, and They Will Come—Working with Industry Allies to Build Successful Continuing Education Programs for Your Hospital**

Kelli Antinori-Lent, Joanne F. Turka, Kathryn Hawkins, Pittsburgh, PA, McDonald, PA

One of the most important responsibilities of inpatient diabetes educators is ensuring patients admitted to the hospital with diabetes are prepared for discharge. Not all hospitals have a diabetes educator on staff. Some, only one. Either way, the educational needs, the training and preparation for discharge, must be addressed. Our 520-bed acute care hospital has 1 diabetes educator. With 40% of all patients having diabetes, a team, not 1 individual, was needed. An interactive, interdisciplinary, entertaining, boot camp-style class was created. The mission: train staff nurses, dietitians, and pharmacists to be both comfortable and confident with teaching diabetes self-management skills at the bedside. The goal: ensure diabetes patients were thoroughly prepared and safe for discharge. The cost of implementing a successful program can be a barrier to program development. To overcome this, diabetes educators who worked in industry were invited to be a part of the program. We worked closely with our Lead Nurse Planner and the Continuing Education office to be certain all policies were followed. To measure the program’s success, a pre-and post-quiz and survey were given to participants. Evaluation of quiz scores demonstrated improved understanding of key patient education information. Evaluation of the surveys reveal improved understanding and confidence with teaching diabetes “survival skills.” Class evaluations are nothing but positive. In 3 years, Diabetes Boot Camp has spread to 5 other hospitals and trained more than 250 nurses, dietitians, and pharmacists. New in 2017, the survey and quiz are mailed to participants 6 and 12 months post-class. This is to evaluate the retention and usefulness of the class over time. A Diabetes Boot Camp 2 was also created. Held once thus far, this class focuses on providing health care providers hands on experience with insulin pumps and sensors as well as learning how to care for hospitalized patients who wear these devices.

---

**You Can Build It, and They Will Come**
703-P
Cost-Effectiveness of Diabetes Self-Management Education and Support in the Community—Projections from a Randomized Controlled Trial
GRETCHEN PIATT, WEN YE, SHIHCHEN KUO, BRANDY R. SINCO, WILLIAM H. HERMAN, MICHAEL S. SPENCER, GLORIA PALMISANO, MICHELE HEISLER, EDITH C. KIEFFER, Ann Altor, MI, Dottor, MD

To impact clinical and behavioral diabetes care, understanding the cost-effectiveness (CE) of diabetes self-management education and support (DSMES/S) in community settings is critical. We aimed to determine the long-term CE of 2 DSMES/S modalities (Community Health Worker (CHW) vs. CHW + Peer Leader (PL)), compared to enhanced usual care (EUC), in reducing risk of diabetes complications in Hispanic adults with type 2 diabetes (diabetes) in metro-Detroit. CE analyses were based on empirical outcome data from a randomized controlled effectiveness trial. Eligible subjects were recruited from one Federally Qualified Health Center and randomized to 1.6 months of CHW-led DSMES + 12 months of CHW-led telephone outreach, 2.6 months of CHW-led DSMES + 12 months of PL-led weekly group sessions with telephone outreach, or 3. EUC. We used the validated Michigan Model for Diabetes to estimate the CE of the 2 DSMES/S modalities compared to EUC over a 10-year simulation time horizon, discounting costs and benefits at 3% annually. Trial-based costs and outcomes were used; other data regarding costs, disease progression, mortality, and utilities were from published literature. From a healthcare sector perspective, CHW+PL was associated with lower costs ($76,599 vs. $77,203 in CHW and $76,779 in EUC) and increased health benefits (quality-adjusted life-years (QUALY): 5.137 vs. 5.108 in CHW and EUC) compared to CHW and EUC, respectively, in the model time horizon. CHW was associated with higher costs but yielded similar QUALYs compared to EUC. The greater intervention costs of CHW + PL were offset by savings arising from averted diabetes complications compared to CHW or EUC. Using CHW+PL for DSMES/S appears to be a sound investment and may be cost-saving for Hispanic adults with diabetes in metro-Detroit.

Supported By: National Institutes of Health

704-P
Introduction of a Web-Based Computerized Personal Diabetes Educational System
KWANG-WEN CHEN, YUH-JUE CHUANG, CHAO KUN LIU, YU-YEN CHIU, HAN-YI LIN, JR., TANYUAN, TAIWAN, TAIPEI, TAIWAN

We established a computerized diabetes educational system which may provide a personal educational advice come after a prior questionnaire. The questionnaire and educational advice were formed by a team of a physician, a dietitian, 3 nurses, and 3 information technology (IT) personnel. The questionnaire comprises the basic data of age, weight, height, and the level of blood pressure, lipid profile, and also the status of retinopathy, nephropathy, and neuropathy. Our IT personnel design the programmatic link between the result of questionnaire and educational advice on website, which using open source software, including Apache software, with Hypertext Preprocessor (PHP) and MySQL database server. The precision and fluency of the advice was modified after repeated discussion on multiple clinical conditions. The final version was first applied on 14 patients (10 men, 4 women), the mean age is 51.6 ± 11.0 years (from 30 to 71 years). Furthermore, a satisfaction survey was performed and showed this system is helpful, feasible, and satisfied to them, also learning motivation was raised.

Conclusion: We developed a web-based computerized diabetic educational system which may provide individualized education, and the system is helpful and feasible to people with diabetes.

Supported By: Kwang-Wen Clinic

705-P
The Efficacy of Registered Dietitian Interventions in Type 2 Diabetes Management in a Family Practice Clinic in North Alabama
BRITTANIE H. CHESTER, WAYNE G. STANLEY, GEETHA THANGAIH, Auburn, AL, Florence, AL

Background: Diabetes self-management education and support (DSMES) and medical nutrition therapy (MNT) have been proven to improve patient outcomes. However, many patients rely on their physician solely for diabetes education despite referrals for diabetes education outside of the physician’s office.

Objective: Our aim was to optimize type 2 diabetes management in a family practice clinic by providing patients with individualized DSMES and MNT by a Registered Dietitian inside of the family practice clinic.

Methods: A random sample of 40 charts was chosen from the electronic medical records of patients with type 2 diabetes completing DSMES and individualized MNT with a Registered Dietitian. Data was extracted from a retrospective chart review on hemoglobin A1C levels before and after appointments with the Registered Dietitian in the family practice clinic from September 2015–November 2015. Analyses were used to assess frequency of patients decreasing their hemoglobin A1C levels, which reveals good glycemic control.

Results: A paired sample t test was performed (n=40). The results revealed that post DSMES and MNT Hemoglobin A1C values (M = 7.64%, SD ± 1.0) were significantly lower than the pre-DSMES and MNT Hemoglobin A1C values (M = 7.17%, SD ± 1.3) (t (40) = 2.89, p < 0.05).

Conclusions: Many healthcare professionals can give dietary advice to patients, but Registered Dietitians are trained to provide individualized nutrition therapy to patients. Combining the knowledge of the physician and registered dietitian can help patients to reach optimal diabetes control in order to prevent or minimize complications. Research has demonstrated a 1% decrease in Hemoglobin A1C levels result in a 21% reduction in diabetes associated mortality, a 14% reduction in myocardial infarction, and a 37% reduction in microvascular complications.

Supported By: Auburn University (to GT)

706-P
Virtual Education for Older Adults with Type 2 Diabetes during Transitions
CHRISTINA R. WHITEHOUSE, JUDITH A. LONG, LORI MCGLEER MALONEY, DAVID A. HOROWITZ, KATHRYN BOWLES, Philadelphia, PA

Compared to older adults without type 2 diabetes (T2D) older adults with T2D have higher rates of hospital admission and readmission. Despite having a diagnosis of T2D, attendance of diabetes self-management education (DSME) classes by older adults is low. Hospitalizations are an opportunity time to engage older adults with T2D, currently no interventions exist utilizing telehealth and DSME for this population during transitions. The purpose of this study is to demonstrate the feasibility of providing DSME through telehealth to older patients with T2D following a hospital admission. We conducted a qualitative study using semi-structured, face-to-face interviews with older adults with T2D engaged in a post-discharge DSME telehealth transitions intervention. Hospitalized older adults (≥ 55 years of age) with T2D were recruited. An advanced practice nurse certified diabetes educator provided one in-person home visit within 48 hours of discharge and weekly DSME sessions via electronic tablet for four additional weeks. After completion of the program, eight patients were asked to describe their experience using the tablet to receive DSME, describe any behavior changes, and if they would accept future education virtual visits. Interviews were audio-recorded, transcribed verbatim and content analyzed thematically. Participants (50% male, aged 57-73 years, 75% African American), cited inconvenience and lack of availability as the leading cause for prior DSME non-attendance. Participants described an increased awareness of dietary habits and more frequent monitoring of glucose. Seven out of 8 participants indicated they would participate in future virtual DSME sessions. Every participant indicated the technology was easy to use and would recommend sessions to others. Our findings support ADA recommendations to improve transitions and to evaluate DSME need at this critical time. Technology use is feasible to enhance availability and convenience for continued DSME in the home after a hospital admission.

Supported By: Tyson Family Endowment; University of Pennsylvania School of Nursing

707-P
Younger Patients with Type 2 Diabetes Have Poorer Self-Care Practices Compared with Older Patients—Results from the Australian National Diabetes Audit
NATALIE NAYAYAKKARA, ANTHONY J. PEASE, SANJEEVA RANASINHA, NATALIE WISCHER, BARBORA DE COURTEN, SOPHIA ZOUNGAS, Clayton, Australia, Chin Chin, Australia

Introduction: Type 2 diabetes is increasingly diagnosed among younger people. Patient engagement with self-care practices is crucial for the optimal management of type 2 diabetes. This study examines the self-care practices of younger and older patients with type 2 diabetes.

Methods: Data were analysed from the Australian National Diabetes Audit (ANDA) that included 2552 adult patients with type 2 diabetes from 56 participating Diabetes Centres. Pre-specified demographic and clinical variables were obtained. Self-care variables (physical activity, following dietary...
recommendations, medication adherence and monitoring blood glucose levels were compared in patients ≤4 years and >64 years of age.

Results: Mean age (SD) of participants was 53±9 years overall, 53±9 years for the younger group and 73±6 years for the older group. Mean diabetes duration was 9±8 years and 15±10 years for younger and older patients, respectively (p<0.01). A greater proportion of older patients reported SMBG levels above 7.0% compared with older patients (76% vs. 68%, p<0.001). A greater proportion of younger compared to older patients reported difficulty following dietary recommendations (50% vs. 32%) and forgetting medications (37% vs. 22%) (all p values <0.001). A smaller proportion of younger compared with older patients reported monitoring their blood glucose levels as often as recommended (60% vs. 70%, p<0.001). Younger age was associated with a 2-fold increase in the odds of not following the recommended self-care practices after adjustment for gender, smoking, insulin therapy, depression and allied health attendance (all p values <0.001).

Conclusion: Despite shorter diabetes duration, younger age was associated with worse glycaemic control and poorer diabetes self-care practices among patients with type 2 diabetes. Targeted strategies are urgently required to optimise diabetes self-care practices and thereby improve glycaemic control.

Implementation and Evaluation of Gestational Diabetes Management Using Mobile Health Care Service—A Pilot Study

MINKYUNG LEE, CHEOL-YOUNG PARK, SUNG-WOO PARK, DA YOUNG LEE, JHEE SUNG, Gyeonggi, Republic of Korea, Seoul, Republic of Korea

Background: Gestational diabetes mellitus (GDM) affects approximately 7% of all pregnancies and is associated with increased risk for the development of diabetes. It is important to recognize and treat GDM to minimize the risk of complications to mother and baby. Multifaceted professional interventions are more effective and mobile healthcare can be one of the good approaches. In this study, we aimed to develop and evaluate the model for prevention and management of GDM using mobile healthcare.

Methods: A total of 21 subjects with no previous history of diabetes, who were diagnosed with GDM during 24-28 weeks of gestation were randomly divided into conventional management group (CM group, n=11) and mobile management group (MM group, n=10). CM group received conventional GDM management and could use mobile application about healthcare freely. MM group received mobile healthcare service including tailored mobile coaching.

Results: Baseline characteristics including HbA1C were not significantly different between the two groups. There were no statistically significant differences in maternal laboratory findings, fetal status and cesarean section rate between the two groups at the time of delivery. Both groups were satisfied with the gestational diabetes management service. Four patients (CM group, n=2 and MM group, n=2) were diagnosed with diabetes by oral glucose tolerance test that followed 4 to 12 weeks after delivery and there was no significant difference in glycated hemoglobin between the two groups. However, postpartum weight and body fat were significantly lower in the MM group.

Conclusions: Mobile healthcare service in patients with GDM showed no significant difference in GDM self-management compared to the conventional management. In addition, it resulted in a significant reduction in maternal weight gain after delivery. Our study showed that mobile healthcare service could be an efficient GDM management tool.

Supported By: Korea Centers for Disease Control & Prevention

Factors Associated with Medication Adherence among Type 2 Diabetes Mellitus Patients in Nepal

PUSHPAJALI SHAKYA, BIRAJ M. KARMACHARYA, ARCHANA SHRESTHA, BAARD E. KULSENG, Dhusikhel, Nepal, Boston MA, Trondheim, Norway

Background: Diabetes is increasing globally resulting in 1.5 million deaths in 2012. The high mortality is due to life-threatening complications of uncontrolled sugar. Medication helps to control glucose level and prevents its complications.

Objective: To identify the factors associated with medication adherence among type 2 diabetes mellitus (DM) patients.

Methods: A hospital based cross sectional study was conducted among 343 patients visiting Dhusikhel Hospital, Nepal for their regular Fasting Blood Sugar test from September to December 2016. Inclusion criteria were 1) type 2 DM patients 2) under diabetes medication from at least past three months 3) aged 18 years or above. We measured medication adherence using Nepali version of 8 item Morisky Medication Adherence Scale (MMSA-B) (4) 2007 Donald E. Morisky). Adherence was categorized as high if MMS score was equal to 8 and moderate/low if it was less than 8. We used standard questionnaire to measure socio-demographic and clinical factors. Multivariate logistic regression was applied to assess factors associated with medication adherence.

Results: Proportion of high and moderate/low medication adherence among the respondents were 60.9% and 39.1% respectively. In multivariate logistic regression, high medication adherence was found to be positively associated with formal education (AOR: 2.43 [95% CI: 1.34, 4.39], p=0.003) and attendance of diabetes counseling [AOR: 1.76 [95% CI: 1.02, 3.04], p=0.04] after adjusting for age, occupation, annual household per-capita income, medicine intake duration and diabetes medicine types. Other variables in the model were not statistically significantly associated.

Conclusion: Formal education and attendance of diabetes counseling were found to positively affect patients’ adherence to medicine. We encourage health care institutions to provide counseling services to all type 2 DM patients and focus more on those who are least educated.

Insulin Titration Algorithms Incorporated into a Patient Glucose Diary Result in Significant Improvements in Glucose Profiles and A1C

MARY L. JOHNSON, DARLENE M. DREON, BRIAN L. LEVY, RICHARD M. BERGENSTAL, Minneapolis, MN, Manlio Park, CA, Wayne, PA

A 44-week, multinational RCT compared efficacy, safety, and subject preference for bolus insulin initiation using a wearable bolus insulin delivery patch (Patch, Calibra Medical) vs. an insulin pen (Pen, NovoLog FlexPen®) in 278 T2D subjects on basal insulin (0.52 U/kg) (A1C: mean ± SD, 8.7% ± 1.0, BMI: 32.6 kg/m², duration: 15 y), using insulin titration algorithms incorporated into a patient diary.

At randomization, basal insulin dose was divided 1:1, basal:bolus. Subjects used SMBG patterns weekly to adjust insulin doses. The diary also included algorithms for adjusting bolus insulin at each meal if SMBG was above or below target and if meal size was larger or smaller than usual.

At 44 weeks there was significant (p<0.001) improvement in A1C with both Patch (mean ± SD 7.0% ± 0.1) and Pen (7.0% ± 0.1). In addition, 7-point SMBG profiles improved dramatically from baseline to Week 44, showing improved fasting glucose and near-normal post-meal values using this set of algorithms (Figure). Total insulin doses increased (Patch: 1.33 U/kg; Pen: 1.38 U/kg), with a basal:bolus ratio of 40:60 in both groups. There was a low incidence of adverse events and hypoglycemia with no difference between groups.

In summary, by making weekly insulin adjustments based on simple algorithms embedded in a patient glucose diary, T2D subjects can significantly improve A1C values and 7-point glucose profiles.

Figure.

7-point SMBG profile

Supported By: Calibra Medical

Diabetes Education via Teacher-Diabetologist Cooperation

SHIZUKA KANEKO, YUMI ONOGI, RYOKO MICHIBATA, Takatsuki, Japan, Reda, Japan

A workforce shortage due to a never before experienced super aged society is coming to Japan. At present, the major producers of society (40-year-olds) are suffering from an increasing incidence of diabetes. Dietary education to S is most important in helping the future labor force develop precautions against life-related diseases before entering the labor force. Student lessons focusing on sugar totals, how to calculate sugar amounts included in bev-
erages, in addition to information on diabetic complications were provided. Problems that occur following severely reduced food intake were also covered. A D provided dietary education to 1100 junior high and high school S on disease development for 3 years in 3 surveys. Shows survey, prior to lectures, over 60% of S were aware of health considerations. However, the decision to eat breakfast was not based on the S’s decision. Some breakfast content was inappropriate due to incomplete knowledge. 50%+ were aware of a health to diet link. Of most interest to S was the amount of sugar contained in sugary drinks. After, many refrained from ingestion of these. Searches found S who had the lesson twice developed their own decision-making ability. 93.7% of S appreciated the knowledge and were pleased to receive knowledge about food intake before suffering disease. They understood why parents said not to take a lot of sugar. 50.1% reviewed food habits, and 82.4% were willing to improve dietary habits. Some students realized they must take personal responsibility for health. 19.3% indicated sharing, or were willing to share this knowledge with others. Some S asked D to advise other S. It is important after receiving education and tracing from Ds that T become the primary interface with S in the passing on of dietary knowledge and advice. T can more consistently pass on this knowledge on an ongoing basis with a view to putting using the knowledge themselves to personal practical use, and then transferring the skills to future generations. D: diabetesologist, T: teachers, S: students.

The Role of Diabetes Educators in Reduction the Risk of Hypoglycemia in Type 1 Patients during Fasting Ramadan

SAHAR MOURAD, Kuwait City, Kuwait

Background/Objectives: Fasting Ramadan for type 1 patients could be a challenging for both patients and physicians due to complications such as hypoglycemia, so in this study we choose to introduce glucose sensor and intensify the role of diabetes educator follow-up for type 1 patients who already on pump and willing to fast Ramadan for the first time.

Design and Methods: This is a pilot prospective cohort study. Total of 6 patients (4 females and 2 males) with type 1 diabetes were recruited. Their mean age is (21.8±2.2) years, diabetes duration (11.1±2.3) years, mean duration on insulin pump is (4±1.6) years. Insulin basal rates of infusion were reduced 5-10% during fasting hours and increased between 5-10% after breaking fast. Weekly follow-up visits during Ramadan took place as well a daily follow-up by phone with the educator. Patients were asked to wear glucose sensor for entire days of fasting to detect hypoglycemia.

Results: An average of 24 hours of basal insulin were set before fasting, and (26.7±6.1) units for 24 hours of basal insulin were required for fasting Ramadan, and from that (15.1±4.3) units was basal insulin for total hours of fasting (14 hours), part of it explained by food habits and lack of activity during Ramadan.

Conclusions: The use of glucose sensor together with adjustment of basal insulin wasn’t enough to minimize the fear of fasting Ramadan but with role of diabetes educator reduce the risk of further hypoglycemia episode.

What Is Detering DSME Service? Perspectives of Diabetes Educators

LINDA M. SIMINERIO, MEGAN HAMM, JODI KRALL, Pittsburgh, PA

Diabetes self-management education and support (DSMES) is considered a cornerstone of diabetes mellitus (DM) care, yet numbers of people receiving DSMES is shockingly low. In response, new delivery models are being implemented in diverse practice sites to improve referral processes and participation. The purpose study was to gain insights from diabetes educators (DEs) providing DSMES in a variety of settings to identify current perspectives on barriers and solutions. Thirty-five DEs from inpatient, outpatient, insurer-based, primary care (PC), specialty practices, and telemedicine models, participated in a focus group facilitated by a skilled moderator. DEs also completed worksheets to get feedback and record views they did not have the opportunity to share in the group. The discussion was transcribed verbatim, and composites to the are summarized to capture dominant themes. DEs expressed feelings of failure in meeting patient needs too late in the course of DM and that primary prevention be considered a major responsibility. DEs perceived that providers under-appreciate DSME services (e.g., think it is limited to nutrition and lifestyle education), consider DSME reserved for complex patients (e.g., comorbidities), and use DSME as punishment for patients with uncontrolled DM (e.g., poor diet). Although DEs in models with direct provider contact had similar sentiments, they found building trust and first hand demonstration of their unique skill set were effective means for changing provider perceptions. For patients, advertising campaigns were recommended to inform patients about the role of the DE and benefits of DSME, particularly at critical and meaningful time points (e.g., starting insulin, disruption in social support).

In summary, findings highlight persistent barriers, namely negative connotations surrounding DSMME and suggest a need for a paradigm shift that supports positive communication to garner appeal for this effective service.

Supported By: National Institute of Diabetes and Digestive and Kidney Diseases

Atypical Antipsychotics and Metabolic Complications

MUNAZA AKUNJIE, SHRUTI M. GHANDHI, ERIC NYLEN, Washington, DC

Introduction: Second generation antipsychotics (SGA) such as olanzapine are often used for psychotic disorders due to their efficacy and fewer neurologic side effects. However, they have been associated with weight gain, prediabetes, diabetes ketoacidosis (DKA), myopathy and rarely rhabdomyolysis. These side effects were reported in individual cases. Our case had both DKA and rhabdomyolysis with chronic olanzapine use of 9 years.

Case: A 36-year-old AAM with schizophrenia on olanzapine and risperidone, diet-controlled hyperlipidemia, obesity and prediabetes (HbA1C 6%), admitted with fatigue, polyuria, polydipsia and confusion. He was diagnosed with DKA with Hba1c 13.7%, rhabdomyolysis (CK 13000 units/L) and acute kidney injury (peak creatinine 12, eGFR<10), requiring insulin infusion, dialysis and mechanical ventilation. Olanzapine was discontinued; his creatinine and glucose improved. His C-epidate was 4.28 ng/ml. Ant-GAD and Ilet cell antibodies were negative. He was discharged on glargine and riperidone. Two months after discharge, Hba1c was 5.8%, creatinine 1 (eGFR<60) and insulin was stopped.

Discussion: This case highlights the importance of monitoring patients on SGA for metabolic complications. Olanzapine’s association with DKA is rare and with rhabdomyolysis is very rare. Several mechanisms for SGA-induced glucose intolerance exist, the most common being the antagonistic effect of olanzapine on serotonin 5HT2C and histamine (H1) receptors in the hypothalamus which leads to increased appetite and weight gain (our patient gained 40 lbs). Additionally, few reports on the association between olanza- zpine and rhabdomyolysis have been published. The mechanism remains unclear but may be due to drug-related myopathy secondary to high affinity for H1, 5-HT2A and D2 receptors. It is possible that the development of DKA predisposed our patient to developing rhabdomyolysis.

Use of Continuous Glucose Monitoring during Dose Adjustment for Normal Eating Course Favors the Emergence of Positive Patient-Provider Language Code

MARCELO DOS SANTOS MAEMED, GIACOMO GASTALDI, SR., Lausanne, Switzerland.

Personalized approach to diabetes care and educations are worldwide recognized to favor health outcomes and health-related quality of life. Continuous glucose monitoring (CGM) can be a powerful tool to help diabetes education. Language and the way clinicians use it has an interactive impact on education.

The aim of the study is to explore the language from the patient-provider interactions mediated by the use of CGM readings. Researchers transcribed and coded the data collected during the seven sessions of Dose Adjustment For Normal eating course taking place at University Hospital of Geneva in Switzerland. The course involved 3 health care providers (dietician, nurse and medical doctor) and 12 participants. All the sessions were filmed and semi-structured interviews of 10 participants and the 3 providers completed the data. Conversation Analysis of the interactive and discursive space created by the narrative’s experiences from participants mediated by CGM readings was investigated as well as Content analysis of the semi-structured interviews in order to put in perspective learning traces through participant’s discourses. The results have shown that health care providers adjust and coordinate their languages through CGM readings in order to organize the narrative’s experiences from the participants. The use of technology reduced judgmental and negative words and promoted the development of a patient-provider narrative useful for learning. The narrative organization clearly impacted the participants. Diabetes technology and particularly CGM readings are powerful tools to develop a specific patient-provider language code promoting effective diabetes education.
Medical Student Knowledge of Current Recommendations for Glucose Screening and Obesity-Related Risk Assessment in Children

EMILY H. GUSEMAN, JONATHON WHIPPS, LAURA L. JENSEN, ELIZABETH A. BEVERLY, Athens, OH

Surveillance data regarding diabetes rates among Appalachian youth are limited. Risk factors for type 2 diabetes among children include obesity, food insecurity, physical inactivity, and familial history. Child obesity runs especially high in Appalachian Ohio, where at least 22% of third graders are obese, compared to 14.3% in suburban counties. In addition to this, one in four children in Appalachian Ohio live below the federal poverty level and many can be expected to have parents with type 2 diabetes, given the high prevalence among adults in the region. Therefore, medical students must be knowledgeable about screening recommendations. We distributed a modified version of the National Cancer Institute’s Physician Survey of Practice on Diet, Physical Activity, and Weight Control: Questionnaires on Childhood Obesity—Related Risk Assessment in Children to osteopathic medical students at one university. Descriptive and frequency analyses were used to analyze students’ knowledge and attitudes related to childhood obesity and diabetes.

Participants in this study were 238 first- through fourth-year medical students (62% pre-clinical, 38% in clinical rotations). Time spent working directly with pediatric patients in a clinical setting differed between pre-clinical and clinical students (21.4 ± 62.0 h vs. 129.7 ± 195.8 h, p < 0.001, respectively). Most students (74%) indicated being unfamiliar with obesity screening recommendations. Few correctly identified BMI percentile cut-points for children overweight (21.2%), obesity (23.7%), and normal weight (50.4%). Students indicated they would initiate glucose screening approximately 4.5 years earlier in overweight/obese patients with risk factors than those with perceived lower risk (p < 0.001).

Although students recognize the need for earlier diabetes screening in children with additional risk factors and/or family history, there is a need to emphasize systematic approaches to diabetes risk reduction in medical school.

Supported By: Ohio University Heritage College of Osteopathic Medicine

718-P

Collaborative Formative Evaluation for Implementation of Primary Care-Based Peer Support in the Shanghai Integration Model

MUCHIEH M. COUFAL, PATRICK Y. TANG, EDWIN B. FISHER, WEPING JIA, Planx, TX; Chapel Hill, NC; Shanghai, China

Peer support (PS) is effective in promoting diabetes self-management, but pragmatic models are needed for specific cultural contexts and healthcare systems. Although rare in China, recent government priorities have created opportunities for PS by encouraging the integration of specialty/hospital with primary/community care. In particular, the Shanghai Integration Model coordinates specialty/hospital care with primary care in Community Health Centers (CHCs), providing an organizational base for implementation of PS. This study reports formative evaluation for PS within the Shanghai model, emphasizing collaboration with CHCs.

Intervention refinement was guided by structured interviews with 15 CHC staff and patients and a focus group with as well as monthly feedback from CHC staff. Based on these, the intervention emphasizes education on medication use, healthy diet, and sustaining physical activity among older adults, and addresses diabetes distress and barriers to insulin treatment.

Results of this collaborative formative evaluation include focus on group as opposed to individual PS with theme-based, interactive activities co-led by CHC staff along with peer leaders. In addition, peer leaders follow-up with individuals and organize neighborhood activities for physical activity, healthy diet, and feelings of comradery.

To date, PS has been implemented in 9 CHCs, involving 74 trained peer leaders, reaching 885 adults. Mean age is 68.24, years with diabetes is 12.52, and HbA1c lower than expected at 7.38%. Counter to common difficulties in reaching men, 41.1% are male. Only 14.2% are taking insulin but 75.3% take oral medications. Important implementation benchmarks include clinician buy-in, high retention, positive participant and peer leader feedback, and extension of programs through engagement with neighborhood residential committees. Collaboration with CHC staff in program refinement have been important in implementation success.

Supported By: Sanofi China; Merck Foundation, Shanghai Municipal Grants (GWIV-3.1)

“IT WAS ALL TRIAL AND ERROR”—THE PERSPECTIVE OF PARENTS OF EMERGING ADULTS WITH TYPE 1 DIABETES DURING THE TRANSITION TO INDEPENDENCE

ANASTASIA ALBANESE-O’NEILL, SARAH C. WESTEN, NICOLE T. THOMAS, MICHAEL J. HALLER, DESMOND SCHATZ, Gainesville, FL, Orlando, FL

Introduction: Emerging adults ages 18-25 years with type 1 diabetes (T1D) navigate the transition to independence in partnership with their parents. Few programs exist to meet the educational needs of parents during this transition, and little is known about their perceived knowledge deficits or readiness to provide guidance for their children. The purpose of this study was to describe the lived experience and diabetes-specific educational needs of parents of emerging adults with T1D.

Methods: Parents of adults with T1D aged 18-25 years were recruited to participate. Written informed consent was obtained and participants then took part in a semi-structured interview. Interviews were digitally recorded and professionally transcribed. A descriptive content analysis of the transcripts began after the first interview and proceeded until saturation was reached. Following the interview, participants were sent links to the study’s diabetes education website that included information on transition topics.

Results: Twenty-two parents (5 fathers, 17 mothers) of emerging adults participated in the study. Six themes emerged from the transcribed interviews: No Roadmap, Few Resources; Peers as Primary Source of Support; New Roles Require a New Communication Style; Parents Sometimes Excluded from Care; Begin Early, Go at the Child’s Pace; and Fears, Challenges, and Opportunities. All participants expressed openness to diverse education modalities, including in person, online, group videoconference, and social media. Participants received 110 push notifications, resulting in 984 page views on the study website.

Conclusions: Parents of emerging adults with T1D have a central role in their child’s transition to independence, but may not receive adequate guidance to be successful in this endeavor. The results of this study underscore the need for a tailored diabetes education program for parents of emerging adults that includes a component of peer support.

Supported By: University of South Florida

716-P

Rapid Improvement of Metabolic Control in Type 1 Diabetes after Transition from Paediatric Clinics to an Adult Diabetes Center

ANNA RITA MAURIZI, SILVIA PIERALICE, DARIO TUCCHINARI, CHIARA GUGLIELMI, ANGELO LAURIA, ERNESTO MADDALUNI, EUFRIA FiORITI, SILVIA MANFRINI, PAOLO FOZZULLI, Rome, Italy

Transition from paediatric to adult diabetes clinics for type 1 diabetes (T1D) patients represents a critical phase often characterized by worsening effects on diabetes outcomes as care visit attendance, metabolic control and diabetes related complications. Aim of this study was to evaluate metabolic control of 122 T1D patients (82.40 M/F, mean SO, age 25.1 ± 5.7 years, disease duration 17.2 ± 8.1 years, HbA1c 7.9% ± 1.4) at time of transition from paediatric clinics to our adult diabetes center. At baseline, 102 patients were on multiple daily insulin injections (MDI) and 20 subjects were on continuous subcutaneous insulin infusion (CSII). The transition process was performed in a specific “transition clinic” according to the protocol of the Consensus Statement of the American Academy of Paediatrics, American Diabetes Association, Academy of Family Physicians and the American College of Physicians. Results after 3 and 6 months follow-up showed a significant improvement in metabolic control with reduction of HbA1c in the whole population (Δ HbA1c -0.3% ± 0.05, Δ HbA1c -0.6% ± 0.05) and this result was confirmed at the end of the study period (HbA1c: 7.9% ± 1.0 vs. 7.1% ± 0.8, p < 0.001). After 6 months since transition 27% of patients were on CSII compared to 16% of patients in the pre-transfer period, however improvement of metabolic control was independent of CSII use.

In conclusion, our data showed that transition from paediatric to our adult diabetes center promotes a very fast reduction of HbA1c already detectable after 3 months of follow-up. This unexpected improvement is likely due not only to increased use of technology but to a more proper clinical setting for emerging adults as recommended by different scientific societies.

Supported By: University of South Florida
The trial showed a reduction of A1c in the intervention group showed non-inferiority in relation to the classical approach. A significant decrease in A1c was observed in relation to the previous six years. A1c levels of the previous six years were collected from clinical records. The statistical procedures were based on ANOVA and Pearson bivariate correlations.

Conclusions: DSME interventions resulted in a statistically significant decrease in mean AIC from 8.5% to 7.7% with a mean AIC reduction of 0.8% in 3 months (p-value<0.01). Mean weight decreased 4.80 lb (p-value<0.0001). 11 remained on same medication, and 1 required reduced insulin. 3 added a glucagon-like peptide receptor agonist (GLP-1RA), with 1 adding a sodium-glucose cotransporter-2 inhibitor. 7 increased daily steps wearing Fitbit, while 8 reported no motivation. 10 increased weekly exercise, and 11 increased daily activity. All benefited from bi-weekly reinforcement, and reported improved nutrition. Food replica models aided visual reinforcement.

Conclusion: DSME in a group setting can motivate self-care and reduce both AIC and weight, however, the study met challenges. Time per patient spent coordinating was substantial. Food models and phone communication to reinforce lifestyle modification were useful. Research is needed to determine what provides long-term sustainability in a busy clinical practice.
Examining the Association between Treatment Satisfaction and Medication Adherence among Patients with Poorly Controlled Type 2 Diabetes

NNADOZIE EMERICHE, NGOZICHUKUWA AGU, MARKU MALMI, JR., JANICE C. ZIHBOR, Tampa, FL

Adherence to diabetes medications remains an important target for public health intervention, however, approximately 32% of people living with diabetes do not take their medications as they should. We examined the association between treatment satisfaction and medication adherence in people living with type 2 diabetes from the ReDesigning MEDIcation Intensiﬁcation Effectiveness Study for Diabetes (REMEDIES 4D) study. REMEDIES 4D was a clustered, randomized trial in which certiﬁed diabetes educators (CDEs) implemented standardized treatment protocols to intensify treatment for glucose, lipid or blood pressure control. Fifteen practices and their patients were randomized to the intervention or usual care. Eligible participants had uncontrolled HbA1c, blood pressure, or LDLc. The intervention group received diabetes self-management education in addition to treatment intensification, while the usual care group participated in monthly support groups for one year. Medication adherence and treatment satisfaction scores were measured using Morisky medication adherence scale and Medication satisfaction survey respectively. A mixed model was created to account for the cluster randomized design and included covariates for treatment status (intervention vs. usual care group), sociodemographic factors, depression, insulin use, count of comorbidities, polypharmacy, baseline clinical values, adherence score at baseline and treatment satisfaction scores 12 months post-baseline. There were 135 participants in the ﬁnal study population (mean age of 60 years and 51% female). After controlling for covariates, treatment satisfaction was associated with an increase in adherence to diabetes medications (β=0.34, p=0.02). Ensuring patients with type 2 diabetes are satisﬁed with their treatment regimen may be a crucial step in improving adherence to diabetes medications.

Supported By: American Diabetes Association (1-12-SAN-31 to J.C.Z.)

Exploring the Type 2 Diabetes Mellitus Experience from the Patient Perspective

KRISTINA YU-ISENBERG, GEOF D. GRAY, CATHERINE FOLEY, JONATHAN T. STOKES, ALAN SHIELDS, GAVIN DICKIE, ROGER LAMOUREUX, CLARK V. JACKSON, BRAD PADILLA, WILLIAM POLONSKY, Boston, MA, Suresnes, France, Del Mar, CA

Introduction: Type 2 diabetes mellitus (T2DM) exacts tremendous burdens on the patient and patient-focused qualitative research can yield data to deepen our understanding of the individual disease experience.

Methods: Research was conducted to illustrate the T2DM patient experience ranging from its proximal signs/symptoms to its distal impacts (e.g., the disease’s impact on physical, social, or emotional functioning). A targeted literature review, meetings with therapeutic experts, and qualitative concept elicitation interviews with T2DM patients were conducted, and results were thematically analyzed and then harmonized into a conceptual model to organize the sign, symptom, and disease-related impact experiences most relevant to T2DM.

Results: A total of 38 unique sign/symptom and 62 impact concepts of T2DM were identiﬁed across the reviewed literature (N=26 publications), expert advice meetings (N=13), and patient interviews (N=20; mean age=60.5±9.5 years, 45% female). The signs/symptoms most frequently reported by both experts and patients were the need to modify diet (n=11 and n=20, respectively), implement an exercise regimen (n=13 and n=17, respectively), and monitor glucose more frequently (n=10 and n=16, respectively). The most bothersome signs/symptoms reported by patients were neuropathy-related (n=8), tiredness (n=5), and vision disorders (n=4).

Conclusions: Patients with T2DM experience many signs, symptoms, and impacts that if improved could give meaningful treatment beneﬁt. Data generated from this research could be used by researchers and healthcare providers to identify treatment outcomes and inform the target concepts of T2DM questionnaires to reliably assess those outcomes.
In a randomized, counter-balanced, blinded study design, we studied 12 recreationally active individuals with T1D (8 males, 4 females, 17.9 ± 3.9 years, HbA1c 7.7 ± 1.0%, mean ± SD). Each completed exercise testing under 3 conditions: euglycemia (5 mM) with basal insulin (20 mU/ml BSA/min) and hyperglycemia (17 mM) with basal insulin and hyperglycemia with low insulin (5 mU/ml BSA/min). The clamp technique was used to achieve study conditions which were maintained for at least 60 min prior to exercise. Standardized exercise performance assessment consisted of 6 tests: a single cycle ergometer VO2 peak test and the following tests performed in triplicate: 6-sec maximal sprint cycling, vertical jump, grip strength, single leg hop test balance, and modified Star Excursion Balance Test. Ten single and choice reaction times were also performed.

Target glucose levels were achieved in all subjects: 4.9 ± 0.03 mM for euglycemia and 17.3 ± 0.04 mM for hyperglycemia (mean ± SE). Mean exercise testing duration was 110 min (range 90–130 min) with no observed ketosis. Analysis of the 6 exercise performance tests using mixed method models did not show any consistent difference in performance between the 3 study conditions. Choice reaction time was slower in hyperglycemia with low insulin compared to the other conditions (p<0.01).

This is the first study to comprehensively assess the effect of acute hyperglycemia on exercise performance. Our findings show that hyperglycemia in either basal or low insulin conditions does not impair exercise performance as measured by a combination of maximal muscle power and strength, postural balance, and maximal aerobic capacity in recreationally active individuals with T1D.
own ICF, adjusted by one of 4 commonly used multipliers: 0%, 50%, 100%, or 150%. At 180 minutes following bolus correction, change in plasma glucose (PG) was greatest in the three arms (15% for T2DM, 7% for T1DM, and -2% for non-diabetic groups). The percentage decrease in PG was greater in the 0% ICF group compared to the 150% ICF group (p<0.05). PG was also significantly lower in the 0% ICF group compared to the 50% ICF group (p<0.05). In conclusion, the use of ICF in the correction of post-exercise hyperglycemia following HIIT is safe and effective. Optimal βG reduction, with no hypoglycemia, occurred in the 100% ICF correction arm.

Figure.
individuals. On two separate days, either 40 IU regular insulin (INS) or normal saline, as placebo (PL), was randomly administered intranasally after overnight fasting, and then each participant underwent a graded exercise test. Indirect calorimetry was used to assess max FOR during exercise and FATmax. Blood insulin and glucose levels did not change after insulin administration. In the N group, max FOR tended to decrease in the INS trial (p = 0.050); FATmax and the total amount of fat oxidation during exercise were significantly smaller in the INS trial than in the PL trial. Max FOR was significantly smaller in the 0 group than in the N group (p = 0.021) and was not influenced by insulin administration. Blood adrenaline levels increased by exercise tended to be reduced by insulin administration in the N group only.

In conclusion, intranasal insulin administration reduces fat oxidation during exercise without increasing peripheral insulin levels, possibly by the suppression of sympathetic nerve activity. The inhibitory effects of intranasal insulin administration on fat oxidation during exercise are diminished in overweight subjects, suggesting cerebral insulin effects are attenuated in this population.

Supported By: Japan Society for the Promotion of Science (JP16K07544), Japan Association for Diabetes Education and Care

Provider Perspectives on Exercise in Children with Type 1 Diabetes

JENIECE IOKOWITZ, MARY PAT GALLAGHER, New York, NY

Background: The benefits of exercise for adults with type 1 diabetes (T1D) are well known but literature in children is limited creating knowledge deficits for pediatric providers and patients. The objective of this study was to determine provider awareness of guidelines, current practices and barriers to counseling during visits.

Methods: Members of the Pediatric Endocrine Society were asked to take an online survey including questions about provider demographics and perspectives on exercise counseling for children with T1D. Descriptive analyses were performed.

Results: A total of 80 providers completed the survey. The majority practice in an urban setting (69%) at academic medical centers (82%). Of respondents, 54% reported they were unaware of exercise guidelines from the American Diabetes Association (ADA) that suggest 60 minutes of exercise daily. Of those who reported awareness, 16 of 37 identified them correctly but only 7 of the 16 reported recommending them clinically. Most providers (40%) reported recommending at least 30 minutes of exercise 5 days per week. The majority reported exercise counseling should be a priority at all visits (65% strongly agree, 30% agree) and cited barriers to counseling were: presence of more pressing issues (76%) and lack of time (61%). Respondents visits (55% strongly agree, 30% agree) and cited barriers to counseling were:

- importance for patients with T1D but time barriers to counseling exist for the majority. Counseling tools that require less time during clinical visits may be beneficial to providers and patients. Also, even respondents who were aware of current guidelines reported recommending shorter periods of exercise. The reason for this discrepancy is unknown but it may reflect the desire to recommend more realistic goals. Further research about the benefits of shorter periods of exercise in this population is needed.

Conclusions: Pediatric endocrinologists report exercise counseling is important for patients with T1D but time barriers to counseling exist for the majority. Counseling tools that require less time during clinical visits may be beneficial to providers and patients. Also, even respondents who were aware of current guidelines reported recommending shorter periods of exercise. The reason for this discrepancy is unknown but it may reflect the desire to recommend more realistic goals. Further research about the benefits of shorter periods of exercise in this population is needed.
with muscle tissue mitochondrial respiration. Our data identify a novel target related to exercise-induced improvements in muscle mitochondrial function and highlight a potential new role for Tribbles 1 in muscle oxidative capacity.

Supported By: Takeda Pharmaceutical Company Limited

741-P

Maintenance of Changes in Glycemic Control and Blood Lipids following 12 Weeks of Underwater Treadmill Training in Adults with Type 2 Diabetes

RYAN T. CONNERS, JOHN M. COONS, DANA K. FULLER, YOUNGDEUK KIM, ROBBIE G. COCHRUM, DON W. MORGAN, Huntsville, AL; Murfreesboro, TN, Lubbock, TX, Osaka, Japan

Objective: To document short- and long-term effects of a 12-week aquatic exercise walking program on glycemic control and blood lipid profile in middle-aged adults with type 2 diabetes.

Research Design and Methods: Thirteen adults with type 2 diabetes (age = 59 ± 4.5 years; 7 females, 6 males) completed 12 weeks of underwater treadmill training (UTT) (3d-wk-1), followed by a 12 weeks of no UTT. During UTT, exercise intensity and duration were systematically and progressively increased from 40-50% of heart rate reserve (HRR) and 30 minutes (3 x 10-min bouts) in Week 1 to 50-70% HRR and 60 minutes (3 x 20-min bouts) in Week 12. During the 12-week period following completion of UTT, study participants were asked to maintain their current diet and allowed to engage in any type or volume of physical activity, with the exception of structured exercise programming. Primary outcome variables included glycosylated hemoglobin (HbA1c), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and the TG/HDL ratio (TG/HDL). Data obtained before UTT, immediately following UTT, and 3 months after the end of UTT were analyzed using 1-way repeated measures analysis of variance.

Results: Compared to baseline values, HbA1c was reduced (7.8% to 7.3%) and HDL-C was increased (43.5 mg/dl to 50.6 mg/dl) following UTT (p < .05). After completion of the 3-month maintenance period, HbA1c was lower (p < .05) compared to baseline (7.4% vs. 7.8%), but HDL-C was not different (p > .05) from the pre-UTT level (48.4 mg/dl vs. 43.5 mg/dl).

Conclusion: Our findings demonstrate that among middle-aged adults with type 2 diabetes, improvement in glycemic control after 12 weeks of underwater treadmill training persisted three months following cessation of UTT, but training-induced increases in HDL were not maintained.

742-P

Combination of Canagliflozin and Exercise Training Leads to Lipid-Dependent Energy Expenditure in Skeletal Muscle in Obese Diabetic Mice

KEICHI TANAKA, HIROKAZU TAKAHASHI, KAZUYO SAGAKI, KANAKO INDO, YAYOI MATSUDA, YUICHIRO EGUCHI, KEIZO ANZAI, HIROKO NISHI, AZAMI SATO, Osaka, Japan

Background and Aim: Sodium-glucose cotransporter 2 (SGLT2) inhibitors exert multiple metabolic effects. Exercise training is a robust treatment of obesity and diabetes, but the effect of SGLT2 inhibitors on exercise training is unclear. We investigated the association between canagliflozin (CAN) and training effects on skeletal muscle and liver in obese diabetic mice.

Method: Male mice loaded with a high-fat diet for 4 weeks were housed in a normal cage (sedentary, sed) or wheel cage (WCR). A total of 0.03%w/w CAN was administered for 2 weeks. Glucose and lipid metabolism of skeletal muscle (gastrocnemius) was analyzed and compared among 4 groups (control/sed, control/WCR, CAN/sed, and CAN/WCR).

Results: Body weight in control/WCR and CAN/sed mice was significantly lower compared with that in control/sed mice, and further weight loss was observed in CAN/WCR mice. There was no difference in running distance between control/WCR and CAN/WCR mice. Control/WCR mice showed lower blood glucose levels than did control/sed mice (P0.042 vs. 231 ± 38.7 mg/dl; p = 0.01). CAN decreased glucose levels, but there was no difference between CAN/sed (118 ± 3.29 mg/dl) and CAN/WCR mice (113.6 ± 4.88 mg/dl). GLUT1 and GLUT4 mRNA levels in skeletal muscle in CAN/sed and CAN/WCR mice were significantly lower than those in control/sed mice. Levels of mRNA of CD39 (1.26) and CD73 (1.28) were significantly higher than those in control/sed mice. PCT1b mRNA levels in CAN/WCR mice were significantly higher than those in CAN/sed mice (p = 0.05).

Discussion: CAN promoted transition from glucose to lipid-dependent energy metabolism in skeletal muscle and this effect might have been enhanced by concomitant exercise.

Conclusion: The combination of CAN and exercise may be effective for weight loss in obesity by an increase in lipid expenditure.

743-P

High-Intensity Interval Training and Hypoglycemia Minimization in Adults with Type 1 Diabetes (HITT HYPO T1D Study)

ANGELA S. LEE, KIMBERLEY L. WAY, NATHAN A. JOHNSON, STEPHEN M. TWIGG, Sydney, Australia

This study examined if reductions in evening basal insulin can minimize overnight hypoglycemia following afternoon high-intensity interval training (HITT) exercise in adults with type 1 diabetes. In a randomized, two-arm crossover trial participants each undertook on separate days: moderate-intensity continuous exercise with 20% overnight basal insulin reduction (CON/T2D), and a series of 3 HIIT isocaloric sessions, with 10% (HITT10), 20% (HITT20) and 30% (HITT30) overnight basal insulin reduction. Post-exercise glucose response was measured by Freestyle Libre Pro Flash Glucose Monitoring, and compared with a non-exercise day (NDN). Participants were given standardised instructions throughout to reduce dinner insulin bolus by 25% post-exercise, have a bedtime snack, and to ensure pre-bed glucose >7.0mM.

Twelve adults participated (9F/3M, 9 MD/3 CSII, mean age 40 ± 4.9 ± 5 years; duration 16 ± 8.9 years, HbA1c 8.0 ± 0.8%, and BMI 26.9 ± 5.2kg/m2).

Whilst overnight glucose profiles were not significantly different across all regimens (Table), the smallest change in glucose from 2300 to 0800 was seen after HITT30, compared with other exercise regimens. Glucose profiles were not significantly different 24h post each regimen (p > 0.28).

Thus, while data suggests HITT30 may be a preferred approach, there were no differences in hypoglycemia rates in exercise regimens applied in this study.

### Table: Overview (2300:0000) glucose profiles by different regimens. Data are means ± SD; glucose in mmol/l.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>NND</th>
<th>CON/T2D</th>
<th>HITT10</th>
<th>HITT20</th>
<th>HITT30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>7.3%</td>
<td>7.1%</td>
<td>7.1%</td>
<td>7.1%</td>
<td>7.1%</td>
</tr>
<tr>
<td>HbA1c</td>
<td>8.0%</td>
<td>7.9%</td>
<td>7.9%</td>
<td>7.9%</td>
<td>7.9%</td>
</tr>
<tr>
<td>Baseline Glucose</td>
<td>7.3%</td>
<td>7.1%</td>
<td>7.1%</td>
<td>7.1%</td>
<td>7.1%</td>
</tr>
<tr>
<td>Post Glucose</td>
<td>6.4%</td>
<td>6.5%</td>
<td>6.5%</td>
<td>6.5%</td>
<td>6.5%</td>
</tr>
<tr>
<td>Baseline Glucose</td>
<td>7.3%</td>
<td>7.3%</td>
<td>7.3%</td>
<td>7.3%</td>
<td>7.3%</td>
</tr>
<tr>
<td>Post Glucose</td>
<td>6.4%</td>
<td>6.5%</td>
<td>6.5%</td>
<td>6.5%</td>
<td>6.5%</td>
</tr>
<tr>
<td>Baseline Glucose</td>
<td>7.3%</td>
<td>7.3%</td>
<td>7.3%</td>
<td>7.3%</td>
<td>7.3%</td>
</tr>
<tr>
<td>Post Glucose</td>
<td>6.4%</td>
<td>6.5%</td>
<td>6.5%</td>
<td>6.5%</td>
<td>6.5%</td>
</tr>
</tbody>
</table>

**Supported By:** Abbott Diabetes Care

744-P

Variability and Reproducibility in the Rise in Blood Glucose Levels in Response to High Intensity Interval Training (HIIT) in Type 1 Diabetes (T1D)—The FIT Reproducibility Study

MICHAEL RIDDELL, RUBIN POONI, RUUTH E. BROWN, LOREN VAVELBERG, ZOEY LI, CRAIG KOLLUMAN, RONNIE ARONSON, Toronto, ON Canada, Tampa, FL

Hyperglycemia can occur when individuals with type 1 diabetes (T1D) perform high intensity interval training (HIIT). However, the reproducibility of the glycemic response to a HIIT session has not been definitively tested. Seventeen patients with T1D, all using insulin glargine 300 U/mL (Toujeo®) as basal insulin, were asked to perform four separate in clinic HIIT sessions in an overnight fasted state. HIIT consisted of two bouts of cycling at 90% peak power, separated by a series of ‘CrossFit’-type activities, spanned over a 25 minute period (~75-95% of maximal heart rate). Plasma glucose (YSI) was measured pre-exercise (~10 min) and at 5- and 15-min in recovery. A total of 64 HIIT sessions were compiled. Pre-exercise blood glucose levels were similar among the four HIIT visits (8.8 ± 1.0 mmol/l, mean SD), as were the rise in glucose levels in response to HIIT (~3.9 ± 1.6; ~3.8 ± 1.8; ~3.9 ± 2.3; ~3.9 ± 1.5 mmol/l, in visits 1-4, respectively). In almost all occasions (63 of 64 sessions), HIIT produced a rise in glycaemia, but the inter-individual responses did vary, ranging from −0.3 to +9.0 mmol/l. The change in glucose during HIIT was not influenced by the baseline glucose concentration and was predictable within an individual based on the measured response in visit 1 (composite correlation with post-exercise glucose rise among the four visits was 0.56 [0.33-0.79, 95% CI]). Following HIIT, there appears to be a consistent increase from the pre-exercise glucose concentration in patients living with T1D and the degree of response is moderately reproducible within a given patient. Individualized insulin correction strategies, which take into account the rise in glucose observed and the patient’s sensitivity to insulin, may be helpful in restoring glucose control after HIIT in patients living with T1D.

**Supported By:** Sanofi
Moderate- and High-Intensity Exercise Training Improve “Free-Living” Glycemic Control Independently of Weight Loss

MICHAEL W. SCHLEH, BENJAMIN J. RYAN, JENNA B. GILLEN, ALISON LUDZKI, JEFFREY F. HOROWITZ, Ann Arbor MI

The independent effects of exercise training (without weight loss) on glycemic control are controversial, and the influence of exercise intensity is not well understood. The aim of this study was to determine the effect of 12 weeks (4 sessions/week) of high-intensity interval training (HIT) or moderate-intensity continuous training (MCT) with weight loss, on “free-living” 24h glycemic control using continuous glucose monitoring (CGM). Eighteen obese adults (33±3 kg m^-2) performed HIT, involving 10 x 1 min intervals at ~90% HR_max interspersed with 1 min recovery (n=8), or MCT, involving 45 min at ~70% HR_max (n=10). CGM was performed under standardized dietary control for 48h before and after training. After training, subjects exercised the day before, but not on Day 1 of CGM measurement. On Day 2 of post-training CGM data collection, participants performed their regular exercise session (HIT or MCT) before breakfast. This approach allowed us to assess the effects of exercise training on glycemic control on a day with and without exercise. On Day 1 post-training, 24h glucose area under the curve (AUC) was modestly lower than pre-training in both groups (HIT: 130±11 vs. 128±7 mM m^-1 h^-1; 24h; MCT: 132±7 vs. 133±7 mM m^-1 h^-1; 24h; p=0.02). There were no differences between HIT and MCT (p=0.22). The improved 24h glycemic control after training was primarily due to modestly lower postprandial responses to breakfast (p=0.03) and dinner (p=0.002), with no differences between HIT and MCT. On Day 2 post-training, which included a session of exercise, glycemic control remained better than pre-training in both groups (p=0.006), but interestingly was not improved further by the acute exercise session (p=0.82 for Day 1 vs. Day 2 post-training).

In conclusion, exercise training improved 24h “free-living” glycemic responses in the absence of weight loss, and in general, the intensity of exercise training did not impact this improvement in glycemic control.

Supported By: National Institutes of Health

Constant-Moderate and High-Intensity Interval Training Induce Differential Metabolic Benefits on Insulin-Sensitive Tissues in High-Fat Fed Mice

SERGIO F. MARTINEZ-HUENCHULLAN, LINDA A. BAN, LUISA F. OLAYA, BABU R. MAHARJAN, CHARMARINE TAM, SUSAN MCLNNAN, STEPHEN M. TWIGGS, Sydney, Australia

Obesity associates highly with metabolic disorders including insulin resistance. To determine if two exercise prescriptions exert differential metabolic benefits in insulin sensitive tissues, we compared isocarboxylase programs of constant-moderate endurance (END) and high intensity interval training (HIT), in a mouse model of diet-induced obesity. Male 10 weeks old C57BL/6 mice were fed a high fat diet (HFD; 45% kcal fat) ab libitum for 10 weeks, achieving 25% excess weight, and for a further 10 weeks they then underwent isocaloric END or HIT (3x40min sessions/week). Untrained HFD mice acted as controls. At 30 weeks of age, mice were sacrificed and quadriceps muscle, subcutaneous adipose tissue (SAT) and liver were excised. Neither END or HIT altered the body weight or the fat/lean mass proportion in HFD mice. An insulin tolerance test (0.65 IU/kgBW) showed HIT but not END improved insulin sensitivity in HFD mice (p<0.05 vs. untrained). In quadriceps, HFD induced down-regulation of high-molecular weight adiponectin protein, which was similarly normalized by END and HIT. In contrast HIT but not END reversed the HFD-driven downregulation of adiponectin receptor 1 (AdipoR1; p<0.05). In SAT, both programs tended to decrease collagen VI protein (p=0.08), whereas only HIT induced an upregulation in mRNA (3-fold vs. HFD untreated) and protein (2-fold vs. HFD untreated) of UCP1. In liver, only END was able to reverse the collagen I accumulation (2-fold; p<0.05) and downregulation of CTGF (0.5-fold; protein) seen in HFD untreated mice (p<0.05). Our results suggest that HIT may promote better systemic metabolic benefits, compared to END during high-fat fed conditions, which could be explained by the normalization of muscle AdipoR1 and higher UCP1 induction in SAT. However, END was more effective in normalizing liver changes, suggesting differential metabolic effects of END and HIT during obesity.

Supported By: National Health and Medical Research Council of Australia; National Commission for Scientific and Technological Research of Chile

Short Sprints during Exercise Reduce Exercise-Mediated Hypoglycaemia in Type 1 Diabetes in a Real-Life Setting

TARINI CHETTY, HEATHER ROBY, NIRRUBASI PARAMALINGAM, JULIE DART, WAYNE SUDIN, GRANT J. SMITH, VINUATH B. SHETTY, PAUL A. FOURNIER, TIM JONES, ELIZABETH A. DAVIS, Perth, Australia

Background: Short sprints have been shown to prevent exercise induced hypoglycaemia in controlled laboratory settings. Using a randomised controlled study design, we tested the hypothesis that incorporating sprinting into moderate intensity exercise can reduce the incidence of exercise mediated hypoglycaemia in individuals with T1D in a real-life setting.

Methods: Individuals with T1D, diagnosed for >1 year, aged 14-35 years, with an HbA1c of ≤9% were recruited into a prospective randomised controlled cross over study. Participants completed three 14-day periods in random order. In one period participants adhered to their usual exercise management (control period), in the other 2 periods, participants additionally incorporated 10s (every 20 mins) or 4s sprints (every 2 mins) into moderate intensity exercise. Outcome measures included the incidence of hypoglycaemia (defined as sensor glucose readings <3.1mmol/L for ≥ 20 minutes) over the 14-day period; and percent time spent <3.1mmol/L and <3.5mmol/L. CGM data were analysed using a mixed model approach.

Results: 24 participants completed the study, performing a total of 420 exercise episodes. The 10s period was associated with fewer hypoglycaemia events (<3.1mmol/L) than the control period (adjusted incidence rate ratio of 0.67; 95% CI 0.46-0.98; p=0.04), with a hypoglycaemia incidence rate of 0.40% (95% CI 0.28-0.55). 33% (95% CI 0.21-0.45) and 0.28% (95% CI 0.17-0.38) events per day in the control, 4s and 10s periods respectively. The 10s period was associated with a reduction in time spent <3.5mmol/L (control vs. 10s period; 3.1% vs. 2.1%; p=0.03) and time spent <3.1mmol/L (control vs. 10s period; 1.9% vs. 1.2%; p=0.03) compared to the control period. There was no increase in nocturnal hypoglycaemia during the sprinting periods.

Conclusion: In a real-life setting the inclusion of 10s sprints into moderate intensity exercise reduces the incidence of hypoglycaemia, without increasing the risk of nocturnal hypoglycaemia.

Supported By: National Health and Medical Research Council of Australia (APP1051229)
Behavioral Medicine, Clinical Nutrition, Education, and Exercise

749-P Exercise Training Alters Sorbin and SH3 Domain Containing 3 DNA Methylation in Human Skeletal Muscle
SAMANTHA E. DAY, LUIS GARCIA, RICHARD L. COLETTA, ELEANNA DEFILIPPIS, LAWRENCE MANDARINO, DAWN K. COLETTA, Phoenix, AZ; Tucson, AZ; Scottsdale, AZ

The physiological changes observed in skeletal muscle following exercise training may be due to epigenetic modifications. Previously, we have shown increased methylation of cytosines (5.0 to 24.4%) in sorbin and SH3 domain containing 3 (SORBS3) in obesity. In another study, we showed decreased methylation (7.6 to -12.4%) of SORBS3 following weight loss induced by bariatric surgery. The aim of this study was to determine whether an exercise training regimen alters DNA methylation of SORBS3. Skeletal muscle biopsies were obtained basally from five insulin-resistant obese (BMI: 32.3±0.8 kg/m2) participants (41.8±3.3 years) before and after 8-weeks of supervised exercise training. After training, BMI and total body weight were unchanged. Training increased peak aerobic capacity (VO2peak) from 20.2±1.9 to 24.3±2.7 mL/kg/min. We performed next generation methylation reduced representation bisulfite sequencing on DNA isolated from the vastus lateralis muscle biopsies. MethylSig analysis revealed 4 cytosines that were decreased in methylation following the exercise training (chr8:22423199: -19.3%, chr8:224242307: -14.6%, chr8:22423252: -27.5% and chr8:22423257: -12.3%, all Benjamini Hochberg q<0.05). All 4 differentially methylated sites fell within the 5’ untranslated region of SORBS3 variant 2. Our results demonstrate that exercise training for 8-weeks in obese participants alters the methylation of SORBS3. To date, we have provided evidence that SORBS3 is epigenetically regulated in skeletal muscle under a number of metabolic conditions including obesity, in response to weight loss by surgical intervention and in response to an 8-week exercise training regimen.

750-P Conversational Artificial Intelligence for Achieving Activity Targets through Routine Physical Activity—Longitudinal Observational Study among People with Type 2 Diabetes
BRU M. MAKKAR, MAAZ SHAH, ABISHEK SHAH, SHILPA JOSHI, BANSHI D. SABOO, ARAVIND R. SOSALE, SR., SV MADHII, RAJIV KOVIL, TEJAS SHAH, MANOJ S. CHAWLA, RAJEV CHHAWLA, JOTHYDEV KESAVADE, Delhi, India; Mumbai, India; Ahmedabad, India; Bangalore, India; New Delhi, India; Trivandrum, India

Objective: People with type 2 diabetes mellitus are prescribed to complete a minimum of 30 mins of activity every day. We evaluate the effectiveness of the Welthy Diabetes (WD) digital therapeutic app in changing health behavior to achieve these activity goals through routine activity, by coaching and nudging them with the help of an artificial intelligence (All powered chatbot).

Methods: De-identified data from 527 users [Mean = 38 years (95% CI: 36.8- 39.3); 69.7% male] who had used the app for at least 21 days and had activity tracking data for at least 15 days was used. The AI-powered chatbot delivered guidance and education on the importance of exercise for persons with diabetes and encouraged users to engage in routine physical activity through personalized nudges and reminders delivered through an AI-Powered digital persuasion model. The WD app tracked the users’ physical activity via inbuilt sensors on the phone.

Results: A total of 46,320 person-days and 8,833 person-weeks of activity tracking was recorded, wherein users were tracked for an average of 87 days (95% CI: 81-95). We recorded the daily active time (DAT) and weekly active time (WAT). Mean DAT was 35 min (95% CI: 33- 37) with a median of 29.75 min (25th-75th: 18-45 min); it was significantly higher for males (37.5 vs. 29.5 min; p<0.001). Mean WAT was 187 min (95% CI: 174-200) with a median of 153 min (25th-75th: 77-242 min). MDAT was noted to be higher on weekdays (38 min) vs. weekends (35 min, p<0.001). Daily active time (DAT) and weekly active time (WAT) were increased significantly (p<0.001) and (p=0.001) respectively in the study period. From baseline, daily active time increased from 32.3±0.8 kg/m2) participants (41.8±3.3 years) before and after 8-weeks of supervised exercise training. After training, BMI and total body weight were unchanged. Training increased peak aerobic capacity (VO2peak) from 20.2±1.9 to 24.3±2.7 mL/kg/min. We performed next generation methylation reduced representation bisulfite sequencing on DNA isolated from the vastus lateralis muscle biopsies. MethylSig analysis revealed 4 cytosines that were decreased in methylation following the exercise training (chr8:22423199: -19.3%, chr8:224242307: -14.6%, chr8:22423252: -27.5% and chr8:22423257: -12.3%, all Benjamini Hochberg q<0.05). All 4 differentially methylated sites fell within the 5’ untranslated region of SORBS3 variant 2. Our results demonstrate that exercise training for 8-weeks in obese participants alters the methylation of SORBS3. To date, we have provided evidence that SORBS3 is epigenetically regulated in skeletal muscle under a number of metabolic conditions including obesity, in response to weight loss by surgical intervention and in response to an 8-week exercise training regimen.

751-P Prediciting Exercise-Related Changes in Glucose in People with Type 1 Diabetes Using Linear Models and Incorporating Knowledge of Prior Exercise
NICHOLE S. TYLER, RAVI REDDY, JOSEPH EL. YOUSSEF, JESSICA R. CASTLE, PETER G. JACOBS, Portland, OR

Exercise-related hypoglycemia in T1D is frequent and can be life-threatening. The ability to predict glucose changes at the start of exercise could significantly improve exercise outcomes for people with T1D. We developed multivariate adaptive regression splines (MARS) to predict changes to blood glucose dynamics and to assess whether including past glucose changes during exercise improves prediction accuracy. Data was collected from 20 adults during a 4-arm, 4-day, outpatient artificial pancreas (AP) study (14 F; weight: 78.3±14.6 kg, age: 35.2±4.8 years, height: 172.0±10.6 cm). Days 1 and 4 of the study consisted of identical controlled meals and aerobic exercise events at an academic medical center. Insulin delivery data, heart rate, continuous glucose measurement (CGM) data, and carbohydrate intake were recorded. Subjects exercised at 60% of their maximal VO2 for 45 minutes. Using the 60 aerobic exercise sessions, 2 linear predictive models were developed to estimate glucose drop during exercise: (1) a model excluding past exercise history (naive), and (2) a model including past exercise (historical). A greedy approach was used to eliminate non-predictive features and build sparse models consisting of CGM at the start of exercise, the rate of change of CGM within 5 minutes of exercise, the metabolic expenditure 5 minutes into exercise, and participant height. Leave-one-out cross validation was done to fit the model and estimate root-mean squared error (RMSE). RMSE was calculated between empirical and predicted glucose drops. The naïve model was able to predict glucose drop to within 18.7 mg/dL. Including historical exercise data improved accuracy and increased RMSE only nominally (naive RMSE=18.7, historical RMSE=17.54). Results demonstrate prediction accuracy of linear models in estimating exercise-related glucose changes with moderate improvement by including prior exercise data.

Supported By: National Institute of Health/National Institute of Diabetes and Digestive and Kidney Diseases (R01DK10175-01A1)

752-P Branched-Chain Amino Acid (BCAA) Metabolism, Insulin Sensitivity (IS), and Liver Fat Response to Exercise Training in Sedentary Prediabetic and Normoglycemic Men
SINDRE LEE, HANNE L. GULSTED, HELGA REFSUM, TORGRIM M. LANGLEITE, TORGER HOLEN, JØRGEN JENSEN, CHRISTIAN A. DREVEN, KARE I. BIRKELAND, Oslo, Norway

Studies suggest a role for BCAA in decreased IS and type 2 diabetes. Exercise improves IS, but the relationship with BCAA metabolism is unclear. We studied the effects of a 12 w exercise intervention on IS, liver fat and BCAA metabolism in prediabetic [n=13] and normoglycemic men [n=13]. We estimated IS by hyperinsulinemic-euglycemic clamp, transcriptomics by mRNA-seq of skeletal muscle and adipose tissue biopsies, liver fat by MRI/MRS, and plasma pBCAA by HPLC, before and after the intervention. At baseline, liver fat and p-BCAA were higher, whereas IS and BCAA skeletal muscle and adipose tissue catabolism were lower in prediabetic vs. control men. Sum of pBCAA were elevated by 14% in prediabetic men and correlated negatively with IS (Figure A, p<0.05). Liver fat and adipose tissue BCAA catabolism correlated significantly to pBCAA levels. The exercise intervention increased IS by 29%, lowered liver fat by 25% and increased BCAA catabolism, whereas no significant change were observed in mean p-BCAA levels and changes did not correlate to changes in IS (Figure B).

In conclusion, exercise intervention did not alter the mean pBCAA, despite significantly improved IS. We suggest that elevated pBCAA levels may not play a direct role causing insulin resistance, but rather is a consequence of accompanying alterations in liver, skeletal muscle and adipose tissue.

Supported By: South Eastern Norway Regional Health Authority
**Improved Metabolic Flexibility Postbreakfast after Exercise Intervention in People with T2DM**

ELVIS A. CARNERO, CHRISTOPHER P. BOCK, NATALIE STEPHENS, RICHARD E. PRATLEY, STEVEN R. SMITH, LAUREN M. SPARKS, Orlando, FL, Cambridge, MA

Exercise provides many metabolic benefits for people with type 2 diabetes; nevertheless, the ability to switch substrate oxidation from fat to carbohydrate and back, known as metabolic flexibility (MetFlex), in response to prolonged exercise training has not been thoroughly explored.

Purpose: The goal of this analyses was to investigate changes in MetFlex after an exercise intervention. We enrolled healthy sedentary participants with obesity (HSDO) and participants with type 2 diabetes (T2DM) in a 10-week aerobic exercise intervention.

Methods: Seventeen participants with T2DM (8 females; 52.9 years; BMI= 36.9 kg/m² and 9 males; 48.8 years; BMI= 33.3 kg/m²) and seven HSDO (5 females; 44.8 years; BMI= 37.6 kg/m² and 2 males; 48.5 years; BMI= 36.2 kg/m²) were invited to participate in the intervention. MetFlex was assessed as the respiratory quotient (RQ) kinetic response after ingesting a standard high CHO breakfast during a 24-hour energy expenditure measurement in a whole-room respiratory chamber. Briefly, the kinetics between the lowest RQ and highest RQ points were analyzed by a simple linear regression between time (1-minute resolution) and RQ units (RQunits/min). Individual data were time-aligned and averaged for each group and moments (PRE and POST intervention), then slopes and intercepts for T2DM vs. HSDO groups and PRE vs. POST were compared using a multiple regression model.

Results: At PRE-intervention, HSDO group had a significantly lower intercept than T2DM (HSDO=-0.737 vs. T2DM=-0.705; P<0.001) and slower RQ kinetics as demonstrated by a greater slope (HSDO=0.0048 RQunits/min vs. T2DM=0.0032 RQunits/min; F=18.1, P<0.001). After the intervention exercise only T2DM significantly increased their slope (POST=0.003944 RQunits/min; F=4.47, P=0.013).

Conclusions: Our results indicate that participants with diabetes significantly improve MetFlex following a prolonged aerobic exercise intervention.

Supported By: American Diabetes Association (7-13-JF-53 to L.M.S.)

---

**Short-Term Interval and Continuous Training Improves Pancreatic β-Cell Function Adjusted for Skeletal Muscle Insulin Resistance in Adults with Prediabetes**

MONIQUE E. FRANCOIS, NATALIE EICHERN, NICOLE M. GILBERTSON, EMILY M. HEISTON, EUGENE BARRETT, STEVEN K. MALIN, Charlottesville, VA

Exercise improves pancreatic function in an energy dose-dependent manner. We previously showed that when calories are matched, an acute exercise bout changes glucose-stimulated insulin secretion (GSIS) relative to multi-organ insulin resistance (IR) in an intensity-based manner during the immediate post-exercise period in people with prediabetes. However, the impact of short-term training intensity on β-cell function is unknown. Thus, we examined the impact of high-intensity interval and moderate-continuous training on GSIS relative to multi-organ IR in adults with prediabetes. Thirty-one adults (Age: 61±8y; BMI: 33±6 kg/m²) were randomized to perform high-intensity interval (INT: 60-min/d alternating 3-min at 90% and 50% HRpeak) or continuous training (CONT: 60-min/d 70% HRpeak) for 2 weeks. Fitness (VO2peak) and body mass were measured before and after, and a 10-min 75g OGTT with blood samples for glucose, insulin, C-peptide and FFA were determined every 30-min. GSIS (C-pep/Glc tAUC0-120min) and β-cell function (Disposition Index [DI: GSIS/IR] relative to skeletal muscle [Insulinratio_x * Glcratio_y] hepatic (HOMA-IR) and adipose (Adipose-IR) IR were calculated. Training increased VO2peak (+1.1±2.1 mL/kg/min), and reduced body mass (-0.6±1.1 kg) and IR (-11.3±7), independent of intensity (P<0.05) INT and CONT also decreased GSIS to a similar extent (Interaction: P=0.88). Short-term training improved skeletal muscle DI by ~24% (P<0.05), but there was no effect on hepatic or adipose DI. Collectively, short-term INT and CONT training improves β-cell function relative to skeletal muscle, but not hepatic or adipose IR. These data suggest unique mechanisms regulate glucose metabolism following single vs. repeated habitual physical activity in adults with prediabetes.

Supported By: National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases (R01DK110175-01A1); Murdoch Foundation
Behavioral Medicine, Clinical Nutrition, Education, and Exercise

POSTERS

Sexual-Dimorphism in Exercise-Induced Beiging and Altered Mitochondrial Function in Inguinal White Adipose Tissue (iWAT) from the Mouse

MARKO DYDANICH, JIE ZHANG, DOROTHY E. VATNER, STEPHEN F. VATNER, Newark, NJ

The goal of this investigation was to examine glucose tolerance and exercise capacity in the regulator of GS protein signaling 14 knock out (RGS14 KO) mouse. Exercise capacity, which affects glucose tolerance, was improved in the RGS14 KO compared to their wild type littermates (WTL), as reflected by a 64 ± 8%, p<0.05, increase in total distance run on a treadmill.

Glucose tolerance was also increased in the RGS14 KO, compared with their WTL, as reflected by a 40 ± 11%, p<0.05, reduction in the area under the glucose curve after administration of 2g of glucose and monitoring blood glucose over the next 3 hours. The insulin tolerance test showed similar improvement in the RGS14 KO as compared to the WTL KO, as reflected by a 47% increase in the insulin index.

To determine if BAT mediated the satiety effects of exercise and glucose tolerance in the RGS14 KO, we simulated a BAT KO, by removing it from the RGS14 KO and transplanting the BAT to their WTL KO. This resulted in a reversal of phenotype, where the WTL with transplanted BAT behaved like RGS14 KO and the RGS14 KO behaved like WTL. The BAT KO with transplanted BAT increased exercise capacity by 36 ± 5%, p<0.05, compared with the RGS14 KO donors. Glucose tolerance showed the same pattern, where WTL with the RGS14 KO BAT transplants exhibited a 39 ± 6% reduction in area under the glucose curve, p<0.05, compared with the RGS14 KO BAT donors. The insulin tolerance test showed similar improvement in the WTL mice with BAT transplant. Thus, there are two mechanisms by which glucose tolerance is enhanced in RGS14 KO: 1. Improved exercise capacity and 2. Increased BAT, suggesting that either inhibiting RGS14 or increasing BAT would be novel therapeutic approaches to protect against diabetes and obesity.

Supported By: National Institutes of Health (HL137268, HL106511)

Two Mechanisms Mediating Enhanced Glucose Tolerance with Regulator of GS Protein 14 Disruption; Increased Exercise Capacity and Increased Brown Adipose Tissue

Moderated Poster Discussion: Nutrition 2018—New Approaches and Practical Realities (Posters: 760-P to 765-P), see page 22.

Effect of Dietary Consumption and Its Fat Content on Glycemic Control and Cardiovascular Risk Factors in Patients with Type 2 Diabetes—A Randomized Controlled Study

ADHAM MOTTALIB, JOANNA MITRI, VERONICA SALSBERG, SAHAR ASHRAFZADEH, TAHAN ELESAIDY, SHAHEEN TOMAH, KHALED ALSIBAI, NOOR MAHMOUD, OSAMA HAMDY, Boston, MA

The 2015 Dietary Guidelines for Americans recommend daily consumption of 3 servings of low or non-fat dairy. However, the effects of dairy consumption and its fat content on glycemic control and cardiovascular risk factors in patients with type 2 diabetes (T2D) are unknown. This study was designed to evaluate the impact of higher consumption of full-fat and low/non-fat dairy on HbA1c, lipid profile and blood pressure (BP) in patients with T2D.

We enrolled 72 participants under controlled T2D (mean age 59±8 years, 46% females) who were consuming <3 servings of dairy/day and randomized them into 3 groups. Group A was asked to incorporate ≥3 daily servings of full-fat dairy and group B to incorporate ≥3 daily servings of low/non-fat dairy into their diet. Group C was asked to maintain the baseline dairy intake. Participants were counseled by a registered dietitian about maintaining their daily caloric intake and body weight. They were asked to maintain their usual doses of diabetes, antihypertensive and hypolipidemic medications. Participants were evaluated at baseline, 3 and 6 months.

At baseline, mean T2D duration was 14±8 years, HbA1c 8.1±1.0%, body weight 92±17 kg, daily caloric intake 1885±680 kcal (43.4±7.0% carbohydrates, 37.8±5.5% fat, 13.0±2.9% saturated fat, and 18.1±3.6% protein), LDL-C 80±26 mg/dL, HDL-C 47±16 mg/dL, triglycerides 172±187 mg/ dL, systolic BP 129±16 mmHg and diastolic BP 72±8 mmHg. There were no differences between groups in any of these parameters at baseline. In the intervention phase, there were significant differences between groups in any of these parameters at baseline. At 6 months, percent calories from saturated fat increased by 3.1±0.8% in group A (p=0.001), and decreased by 4.4±1.7% in group B (p=0.014). There were no differences in HbA1c, body weight, total caloric intake or percent calories from carbohydrates, lipid parameters or BP between groups.

Two Years Superserved Resistance Training Prevented Diabetes Incidence in People with Prediabetes—A Randomized Control Trial

Objective: To explore the long-term effects of aerobic training (AT), resistance training (RT) and both (AT+RT) on prevention of incidence of type 2 diabetes (T2D) in patients with prediabetes.

Methods: Randomized control trial conducted in two Chinese medical centers between October, 2014 and November, 2016. Of 724 subjects, 122 declined, 430 were excluded, and 172 with prediabetes (fasting glucose ≥5.6mmol/L and/or 2-hour glucose ≥7.8mmol/L and/or <11.1mmol/L in the 75g oral glucose tolerance test) were included for randomization. Supervised exercise programs including AT, RT and AT+RT were completed for 60 minutes, three consecutive times per week for 24 months respectively.

Primary outcome was incidence of T2D, secondary outcomes included hemoglobin (HbaA1c), fasting plasma glucose (FPG), standard 2-hour oral glucose tolerance (2hPG), and lipid profile.

Results: 137 (80%) subjects, mean age 59 years, 45 men, 92 women, entered final analysis. After 24 months of intervention, the incidences of T2D adjusted by sex and age were significantly decreased by 74% (95% CI 0.38-0.89%), 85% (95% CI 0.21-0.85%) and 72% (95% CI 0.36-0.87%) with AT, RT, and AT+RT, compared with control group (HRR 0.26(95% CI 0.11-0.62) in AT+RT 0.35(0.15-0.79RT), and 0.289(95% CI 0.13-0.64)AT), and the cumulative T2D incidences were significantly lower in AT+RT, RT, and AT group, compared to that of the control group (21%, 26% and 22% vs. 69%). Blood glucose and lipid profile in AT, RT and AT+RT improved more than in the control group, which had prevailed over time.

Conclusions: Resistance training and resistance training plus aerobic training were as effective as isolated aerobic training in preventing progression to T2D. Patients with prediabetes can choose aerobic training, resistance training or both to prevent T2D. This can have substantial impact on engaging patients with lifestyle change to prevent or delay T2D onset.

Support: National Institutes of Health (HL137268, HL106511)
Evaluation of Dietary Intakes of Macronutrients in Adults with Different A1c Levels

OWEN KELLY, JESSICA L. KROK-SCHOEN, MENGHUA LUO, CHRISTOPHER A. TAYLOR, Columbus, OH

Nutritional modification is a key consideration for the management of diabetics. Characterization of dietary habits among adults with diabetes may help focus dietary behavior changes. Dietary intakes and hemoglobin A1c data from the 2005-2014 National Health and Nutrition Examination Survey (NHANES) were evaluated to assess differences in meal and snacking macronutrient patterns by A1C levels. Data from 20,206 adults ≥ 30 years were categorized into the following groups using A1C values: <5.7% (nondiabetes, n= 12,949); 5.7-6.4% (prediabetes, n=4,892); 6.5-9.4% (controlled diabetes, n=7,680); and ≥7%, poorly controlled diabetes, n=1,597). Dietary intakes were assessed via a 24 hour dietary recall. Eating occasions were defined by the participant. Data analyses were weighted to create a nationally representative sample. Overall, the mean energy intakes were higher in the nondiabetes group by up to 264 kcal. Mean protein, carbohydrate and fat intakes were also higher in the nondiabetes group. Intakes for energy and macronutrients were similar across all groups at breakfast and dinner, however, at lunch and for all snacks combined, those without diabetes had higher intakes. Intakes of added sugars at eating occasions were also higher in the nondiabetes group and snacks contributed the most for all groups. The daily total number of carb choices for the nondiabetes, prediabetes and both diabetes groups were 17, 16, 15 and 15, respectively. For all groups, dinner was the largest meal and accounted for the highest carb choice values. Despite the overall reduction in energy and macronutrient intakes in those with elevated A1c, indicating they may be making perceived positive dietary behavior changes, all the groups diets are low in quality per Healthy Eating Index. There may need to be a greater focus on changing macronutrient quality, especially carbohydrates, when developing individualized medical nutrition therapy for people with diabetes or prediabetes.

Supported By: Abbott

Impact of the ENHANCED (diEtitianNs Helping ATPieNts CarE for Dia­betes) Trial on Optimal Care Outcomes in Adults with Type 2 Diabetes

GRETCHEN BENSON, ABBEY SIBBERTO, JOY HAYES, JACKIE L. BOUCHER, MARC VACCCHAR, MICHAEL D. MIEDEMA, ARTHUR SILLAH, JEFFREY VAN-WORMER, Minneapolis, MN; Seattle, WA; Madison, WI

Background: Clinical care for type 2 diabetes has improved, but remains suboptimal. Collaborative, team-based models that maximize the skills of different disciplines may improve care for type 2 diabetes, but few have been tested using rigorous research designs.

Objective: We investigated the effectiveness of a registered dietitian nutritionist-led (RDN) telemedicine program vs. usual care on type 2 diabetes optimal care goals, including A1C, blood pressure, tobacco use, and appropriate statin and aspirin use. For participants randomly assigned to the intervention group, RDNs utilized an approved treatment protocol to initiate/titrate therapies for blood glucose, hypertension and lipids, in addition to providing medical nutrition therapy. Outcomes were compared between the intervention vs. usual care group over one year.

Design: A randomized control trial design was used that included 118 adults with type 2 diabetes who were receiving care at two rural primary care clinics. Participants were randomized (March-December 2016) to usual (clinical) care or an intervention group that included usual care plus monthly RDN-led telemedicine visits for one year.

Results: Mixed model regression was used to examine outcomes between baseline and one year follow-up. Modest, but significantly greater improvement was observed for the intervention group in the number of optimal care measures met at follow-up, 3.7 compared to 3.2 among controls (p=0.017) after adjusting for baseline. Among individual optimal care measures, the intervention group had a significantly greater increase in medication use, with 2.5 and 2.2 higher odds (compared to controls) of taking a statin and aspirin as appropriate, respectively.

Conclusions: The ENHANCED study care model, which utilized RDNs to initiate and titrate medications, modestly improved type 2 diabetes care outcomes for adults.

Supported By: Diabetes Care and Education Dietetic Practice Group/Academy of Nutrition and Dietetics Foundation

This study shows that increasing consumption of dairy products to ≥3 servings/day, irrespective of fat content, has no effect on HDL cholesterol, lipid profile or BP in patients with T2D.

Supported By: National Dairy Council

Comparison of Effects of Low-Carbohydrate Diet and Calorie-Restricted Diet on Nonalcoholic Fatty Liver Disease in Japanese Patients with Type 2 Diabetes

EITA NISHIMORI, SATOSHI OGATA, MUTUJO NAKA, Nagano, Japan

Background: Nutrition therapies for type two diabetes (T2DM) and nonalcoholic fatty liver disease (NAFLD) are recommended for calorie-restricted diet (CRD) in Japan. Recently, the efficacy of low-carbohydrate diet (LCD) has been reported in these diseases. This study aimed to determine the effects of LCD on NAFLD in Japanese patients with T2DM compared with CRD.

Methods: We assigned 26 patients of NAFLD with T2DM in this 3-month prospective open-label randomized comparative trial. They were randomly allocated to either LCD (70-130 g/day of carbohydrate) group (n =14) or CRD (calories of 25 kcal/kg of ideal body weight per day) group (n =14). Abdominal computed tomography (CT) scan evaluated liver fat deposition by the liver-to-spleen attenuation ratio (L/S ratio) and visceral fat accumulation as the visceral fat area (VFA).

Results: The average age of patients at the start was 50 years old, BMI was 31 kg/m2, L/S ratio was 0.7, VFA was 163 cm2. The total intake energy of LCD after 3 months was 1,389 kcal (±386 kcal from the start, carbohydrate was 42% of the total energy), CRD was 1,513 kcal (±533 kcal, carbohydrate was 54%). Both diets achieved significantly improvement of L/S ratio, VFA, liver transaminase, body weight and HbA1c from baseline within groups after 3 months (p < 0.05). Between the two diets, L/S ratio, liver transaminase, body weight and HbA1c showed a large tendency to improve in LCD, but no significant difference was noted. Significant improvement was observed in VFA of LCD. In the DQI score, “anxiety and dissatisfaction with treatment” was significantly improved in LCD.

Conclusions: Our findings suggest that LCD may be as effective as CRD in improving fatty liver in Japanese patients of NAFLD with T2DM, and that LCD may be less burdensome on patients than CRD.

Dietary Protein Intake Is Not Associated with Progression of Diabetic Nephropathy in Patients without Macroalbuminuria

AYUMI KAJI, YOSHIKATA HASHIMOTO, RYOSUKE SAKAI, TAKURO OKAMURA, MASAKI YAMAZAKI, MICHIAKI FUKUI, Kyoto, Japan

Background/Aims: Diabetic nephropathy is an important problem in patients with diabetes. However, little is known about the effect of dietary protein intake on albuminuria in patients with diabetes. Thus, the aim of this study was to clarify the association between dietary protein intake and change in urinary albumin excretion (UAE) or estimated glomerular filtration rate (eGFR) in patients with type 2 diabetes.

Methods: In this retrospective cohort study, we included 143 patients (71 men, average 64.0 (10.5) years, and median 14.5 (6.7-38.5) mg/gCr) without macroalbuminuria (UAE over 300 mg/gCr). Change in UAE or eGFR was categorized to either LCD (70-130 g/day of carbohydrate) group (n =14) or CRD (calories of 25 kcal/kg of ideal body weight per day) group (n =14). Abdominal computed tomography (CT) scan evaluated liver fat deposition by the liver-to-spleen attenuation ratio (L/S ratio) and visceral fat accumulation as the visceral fat area (VFA).

Results: The average age of patients at the start was 50 years old, BMI was 31 kg/m2, L/S ratio was 0.7, VFA was 163 cm2. The total intake energy of LCD after 3 months was 1,389 kcal (±386 kcal from the start, carbohydrate was 42% of the total energy), CRD was 1,513 kcal (±533 kcal, carbohydrate was 54%). Both diets achieved significantly improvement of L/S ratio, VFA, liver transaminase, body weight and HbA1c from baseline within groups after 3 months (p < 0.05). Between the two diets, L/S ratio, liver transaminase, body weight and HbA1c showed a large tendency to improve in LCD, but no significant difference was noted. Significant improvement was observed in VFA of LCD. In the DQI score, “anxiety and dissatisfaction with treatment” was significantly improved in LCD.

Conclusions: Our findings suggest that LCD may be as effective as CRD in improving fatty liver in Japanese patients of NAFLD with T2DM, and that LCD may be less burdensome on patients than CRD.

Table. Multiple Regression Analysis of ΔUAE or ΔeGFR

<table>
<thead>
<tr>
<th>Variable</th>
<th>ΔUAE Standardized β</th>
<th>p Value</th>
<th>ΔΔGFR Standardized β</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log(UAE+1)</td>
<td>0.217</td>
<td>0.012</td>
<td>0.094</td>
<td>0.560</td>
</tr>
<tr>
<td>Protein intake (g/kg/day)</td>
<td>-0.064</td>
<td>0.454</td>
<td>-0.033</td>
<td>0.698</td>
</tr>
<tr>
<td>Usage of RAS inhibitor</td>
<td>0.114</td>
<td>0.193</td>
<td>-0.022</td>
<td>0.201</td>
</tr>
<tr>
<td>Cr (mg/dl)</td>
<td>0.047</td>
<td>0.046</td>
<td>0.388</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>-0.003</td>
<td>0.977</td>
<td>0.061</td>
<td>0.490</td>
</tr>
<tr>
<td>BMI</td>
<td>0.119</td>
<td>0.184</td>
<td>-0.042</td>
<td>0.634</td>
</tr>
<tr>
<td>Men</td>
<td>-0.143</td>
<td>0.163</td>
<td>0.121</td>
<td>0.237</td>
</tr>
</tbody>
</table>

ADA-Supported Research

Moderated Poster Discussion
Bacterial Characteristics of the Vitamin D and Type 2 Diabetes (D2d) Study—A Contemporary Prediabetes Cohort
ERIN LEBLANC, RICHARD E. PRATLEY, BESS DAWSON-HUGHES, MYRENE A. STATEN, PATRICIA A. SHEEHAN, MICHAEL R. LEWIS, ANNE L. PETERS, SUN H. KIM, RANEE CHATTERJEE, VANITA ARID, CHAIWAR CHADINA, ANASTASSIOS PITTAS, Portland, OR; Orlando, FL; Boston, MA; Madison, VA; Burlington, VT; Los Angeles, CA; Stanford, CA; Durham, NC; Hyattsville, MD; Saint Paul, MN
Objective: Describe baseline characteristics of the NIH/ADA-supported D2d study, the first diabetes prevention trial in the U.S. to currently apply ADA diagnostic glycemia criteria.

Research Design and Methods: Multicenter (22 sites), randomized, double-blind, placebo-controlled, primary prevention trial testing efficacy of oral daily 4000 IU cholecalciferol (D3) compared to placebo on incident diabetes in adults at high risk. Eligible participants met at least 2-of-3 2010 ADA glucose criteria for prediabetes: fasting plasma glucose (FPG) 100-125 mg/dL, 2-hour glucose post-75g oral glucose load (2hPG) 140-199 mg/dL, and/or hemoglobin A1c (HbA1c) 5.7-6.4%.

Results: 2423 participants (45% women, 33% non-white) were randomized. Mean (±SD) age was 59 (±9) years, and BMI was 32 (±5) kg/m². Thirty-five percent met 3 prediabetes criteria, 49% met FPG/HbA1c criteria only, 9.5% met 2hPG/FPG criteria only, and 6.3% met 2hPG/hbA1c criteria only. Black participants had higher HbA1c and lower FPG concentration than white, Asian, and other races (P<0.01). 2hPG concentration did not differ by race (Table). The D2d cohort has lower 2hPG but similar HbA1c and FPG concentrations than previous prediabetes cohorts.

Conclusions: D2d will establish the efficacy and safety of vitamin D supplementation for diabetes prevention and inform on the natural history of prediabetes per contemporary ADA criteria.

Table. Glucose profile of the D2d prediabetes cohort by CAST subtypes and ethnicity

<table>
<thead>
<tr>
<th>Glucose Profile</th>
<th>N</th>
<th>White</th>
<th>Asian</th>
<th>black</th>
<th>Other</th>
<th>Prediabetes (n=2423)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG (mg/dL)</td>
<td>2423</td>
<td>105.9±12.4</td>
<td>108.4±12.7</td>
<td>111.3±12.7</td>
<td>105.1±12.7</td>
<td>108.4±12.7</td>
</tr>
<tr>
<td>2hPG (mg/dL)</td>
<td>2423</td>
<td>146.0±44.9</td>
<td>147.1±44.9</td>
<td>139.0±44.9</td>
<td>148.0±44.9</td>
<td>147.1±44.9</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>2423</td>
<td>5.6±0.8</td>
<td>5.6±0.8</td>
<td>5.6±0.8</td>
<td>5.6±0.8</td>
<td>5.6±0.8</td>
</tr>
</tbody>
</table>

Safer Glycemic Control Using Fructose-Based Enteral Formula—A Randomized Crossover Clinical Trial
MAIGALI KUMBIER, CASSIANO TEIXERA, LUCAS HELAL, JUSSARA ALMEIDA, Porto Alegre, Brazil

Background: Glycemic control during nutritional therapy in patients under intensive care has shown a great importance in relation to morbidity and mortality. To avoid glycemic oscillation in patients under enteral nutrition, usually a low-carbohydrate diet is offered, but differing among themselves by carbohydrate type. A question that remains unanswered is whether the presence of fructose interferes with glycemic oscillation or not.

Objective: The aim of this clinical trial was to evaluate the effect of two diabetes-specific diets (fructose-based vs. maltodextrin-based) in the glycemic variability of critically ill patients.

Materials and Methods: This is a randomized, active-controlled, double-blind crossover clinical trial comparing diabetes-specific enteral formula with and without fructose in critically ill patients. Twenty-five patients, who developed hyperglycemia during intensive care unit stay, were included. Patients were randomized to receive each diet for 2 days. Capillary blood sample was taken every 4 hours and glycemic variability was defined as the difference between each time point. A significance level of 0.05 was defined for all statistical inferences.

Results: Patients which underwent the fructose-based diet reduced their glycemic variability against that under usual care overtime -11.92 mg/dL (95% CI -19.22 to -4.63 mg/dL), p = 0.0013 for between-group differences. We observed also some differences on specific time frames, especially in measures 6, 8, and 12. This effect was seen without any risk of hypoglycemia and complications.

Conclusions: Diabetes-specific enteral formula with fructose was associated with lower glycemic variability in critically ill patients when compared to diabetes-specific enteral formula without fructose.
Relationship of Vitamin B12 and Homocysteine Status with Nephropathy and Neuropathy in Metformin-Treated Patients with Type 2 Diabetes

SHRVAJIRAO PATIL, ROMAN PAWLAK, APARNA THOMBARDE, RICHARD BAL- TARD, KRISTIE HICKS, DOYLE M. CUMMINNS, Greenville, NC

Limited evidence suggests that both vitamin B12 (B12) and homocysteine (Hcy) status are impacted by metformin use and may be associated with diabetes complications. The goal of this research project was to assess the cross-sectional association between B12 and Hcy status and kidney function and neuropathy among patients with type 2 diabetes (T2D) taking metformin. Adult patients in an academic primary care clinic (n = 52; mean age = 53 ± 12.5 years; female 56%; African American 70%) with T2D (mean duration = 9.8 years) and taking metformin (mean duration = 9.2 year) provided informed consent and had blood and urine specimens drawn for: Alc, B12, Hcy, serum creatinine (sCr), urine albumin/creatinine ratio, and eGFR. Neuropathy was assessed using the validated Michigan Nephropathy Screening Instrument. Mean B12 and Hcy levels were 568.7 pg/ml and 12.85 µmol/L, respectively. Serum B12 was significantly correlated with Hcy (r = −0.3, p = 0.035) and with Alc (r = 0.36, p = 0.01). Hcy was significantly correlated with both sCr (r = 0.70, p = 0.0001) and eGFR (r = −0.68, p = 0.0000). While B12 was not directly correlated with either diabetes duration or duration of metformin therapy, the correlation of B12 with total metformin exposure (dose x years) approached significance (r = −0.26, p = 0.08). There was no relationship of either B12 or Hcy with neuropathy scores. The bivariate relationship of B12 and Hcy to renal function measures was not different in patients with a diabetes duration of less than 10 years vs. 10 or more years. Consistent with previous studies our findings suggest that B12 status, in addition to correlating with renal function, correlated with glycemic control. Periodic measurement of B12 status should be considered in metformin-treated patients with T2D.

Supported By: East Carolina University

Impact of the No-Carrageenan Diet on Glucose Tolerance and Insulin Resistance in Adults with Prediabetes

JOANNE K. TOBACMAN, Chicago, IL

Previous animal and cell-based studies indicated that exposure to the common food additive carrageenan impaired glucose tolerance and increased insulin resistance. Carrageenan is widely used in processed foods to improve solubility, but predictably causes inflammation, which contributes to insulin resistance by inhibition of insulin signaling. To test if removal of carrageenan from the diet could reduce insulin resistance, we initiated a double-blinded, controlled feeding study in individuals with prediabetes, defined by HbA1c 5.7%-6.4%. All procedures were approved by the University of Illinois at Chicago IRB. Participants were provided study diets for 12 weeks, which either contained or did not contain carrageenan, and had similar composition of protein, carbohydrate, and fat. An additional group of 15 subjects with normal glucose tolerance (NGT) and 29 type 2 diabetic patients. A 500-kcal meal tolerance test, using white rice alone (white rice) or barley. Subsequently, a meal tolerance test with identical carbohydrate quantity (52g carbohydrate) with or without 1.8g of β-glucan, was performed, and plasma glucose (PPG) regulation in the management of type 2 diabetes. Viscous dietary fibers including oat and barley β-glucan are one of the most effective classes of functional food ingredients for reducing PPG. We investigated the effect of high β-glucan barley on postprandial plasma glucose and C-peptide levels using a meal tolerance test and continuous glucose monitoring (CGM) in 15 subjects with normal glucose tolerance (NGT) and 29 type 2 diabetic patients. A 500-kcal meal tolerance test, using white rice alone (white rice) or white rice mixed with 50% of barley (Kirari-mochi®) containing 1.5-times β-glucan, was performed, and plasma glucose and C-peptide levels were measured every 30 minutes for 180 minutes. Daily glucose variability was measured using CGM over two days, while subjects consumed 1600-kcal or 1800-kcal test meals consisting of white rice or barley. Subsequently, a meal tolerance test with identical carbohydrate quantity (52g carbohydrate) with or without 1.8g of β-glucan, was performed in 7 diabetic patients. In NGT subjects and diabetic patients, the incremental area under the curve (AUC) of plasma glucose and C-peptide levels for 180 minutes after the meal tolerance test were significantly decreased following the consumption of barley compared to the consumption of white rice alone. The studies using CGM have demonstrated that the consumption of barley lead to a significant decrease in the 24-h standard deviation of blood glucose (24-h SDBG) and mean amplitude of glycemic excursion (MAGE) in diabetic patients. Similar results were obtained in subsequent tests with identical carbohydrate quantity but with β-glucan.
In conclusion, these results suggest that high-glutam barley may contribute to decreased PPG levels and endogenous insulin secretion in both patients with type 2 diabetes and the subjects with NIGT.

773-P

Effect of Reduced Intake of Branched-Chain Amino Acids (BCAA) on Insulin Secretion and Sensitivity in Type 2 Diabetes

YANISLAVA KARUSHEVA, THESA VAN GEMERT, MARIE-CHRISTINE SIMON, DANIEL F. MAR'KGRAF, KLAUS STRASSBURGER, DIETMER SCHMOLL, VULKER BURKART, KARSTEN MÜSSLING, JULIA SENZREDIG, MICHAEL RÖDEN, Düsseldorf, Germany, Bonn, Germany, Frankfurt, Germany

OBJECTIVES: Elderly patients with type 2 diabetes is increasing and sarcopenia is becoming an important problem. Nutrition is important to protect sarcopenia. However, the relationship between energy intake and sarcopenia is becoming an important problem. In conclusion, short-term dietary reduction of BCAA decreases meal-induced insulin and C-peptide secretion, increases FGF-21 levels and stimulates mitochondrial efficiency in adipose tissue, but fails to improve IS in T2D.

Supported By: Sanofi Aventis Deutschland GmbH

774-P

Reduced Energy Intake Is Associated with Sarcopenia in Elderly Patients with Type 2 Diabetes—Kamogawa-DM Cohort Study

TAKURO OKAMURA, YOSHIKATA HIKISHI, RYUSUKE SAKAI, EMU USHIGOME, MASAHIDE HAMACHI, MASASHIRO YAMAZAKI, MICHIAKI FUKUI, Kyoto, Japan

OBJECTIVES: Elderly patients with type 2 diabetes is increasing and sarcopenia is becoming an important problem. Nutrition is important to protect sarcopenia. However, the relationship between energy intake and sarcopenia in elderly patients with diabetes has been unclear.

Research Design and Methods: In this cross-sectional study of 316 patients (181 men and 135 women), we investigated the relationship between energy intake and sarcopenia in elderly patients with diabetes mellitus as well as healthy people. However, few reports have shown TEE in patients with diabetes, particularly in Asian countries. Therefore, we evaluated accurate TEE by doubly labeled water (DLW) and physical activity level (PAL) in Japanese patients with diabetes mellitus.

Methods: We planned to recruit sixty patients with type 2 diabetes and sex- and age-matched twenty nondiabetic subjects as the CLEVER-DM Study at a single university hospital. The current presentation is a part of this study with forty-one patients with type 2 diabetes (DM, 69.9 years, men/women: 23/18) and nine patients without DM (non-DM, 67.2 years, men/women: 2/7). TEE was measured over 14 days by DLW method and PAL was calculated as TEE divided by resting energy expenditure assessed by indirect calorimetry.

Results: The numbers of DM patients treated with insulin, oral hypoglycemic agents, and diet/exercise were 13 (31.7%), 20 (48.8%), and 8 (19.5%), respectively. Mean (standard deviation) level of HbA1c was 6.9 (0.8%) for DM and 5.5 (0.4%) for non-DM (p<0.001). Mean (SD) body mass index was 23.2 (2.9) kg/m² for DM and 23.1 (1.9) kg/m² for non-DM. After adjusted for age, sex, fat-free mass, and fat mass, mean TEE was 2150 kcal/day for DM, and 2087 kcal/day for non-DM, and there was no significant difference between two groups, although DM tended to have a higher value (mean difference: 83 kcal/day, 95% confidential interval [CI] -101 to 267 kcal/day). Mean PAL adjusted for sex and age was 1.68 for DM and 1.83 for non-DM, showing no statistical differences (mean difference: 0.04, 95% CI: -0.07 to 0.15).

Conclusion: TEE was comparable between DM and non-DM groups among Japanese.

Supported By: Japan Agency for Medical Research and Development

Table. Clinical characteristics of study patients

<table>
<thead>
<tr>
<th></th>
<th>Patients with sarcopenia (n=39)</th>
<th>Patients without sarcopenia (n=277)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>19/20</td>
<td>162/211</td>
<td>0.251</td>
</tr>
<tr>
<td>Age (year)</td>
<td>74 (6.4)</td>
<td>70 (4.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>50.9 (8.5)</td>
<td>52.6 (11.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>21.0 (3.0)</td>
<td>24.5 (3.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lean/normal/overweight/obesity</td>
<td>9/10/80/10</td>
<td>11/100/80/95</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Appendicular muscle mass (kg)</td>
<td>13.8 (3.9)</td>
<td>18.2 (4.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Skeletal muscle mass index (kg/m²)</td>
<td>5.7 (0.7)</td>
<td>7.0 (1.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grip Strength (kg)</td>
<td>16.5 (5.2)</td>
<td>28.1 (8.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking (non-current smoker)</td>
<td>35/4</td>
<td>192/85</td>
<td>0.870</td>
</tr>
</tbody>
</table>

775-P


KEIKO KONDO, KATSUTAKO MORINO, SHIGEHO TANAKA, KEIKO FUJISE, AKIKO OHI, MIKA KIRIHARA, MASAYA SASAKI, FUMINORI KATSUKAWA, HIROYOSHI MAEGAWA, Otsu, Japan, Shinjuku, Japan, Shiga, Japan, Yokohama, Japan

Background and Aim: Assessment of total energy expenditure (TEE) is essential for recommendations for dietary intakes and physical activity in patients with diabetes mellitus as well as healthy people. However, few reports have shown TEE in patients with diabetes, particularly in Asian countries. Therefore, we evaluated accurate TEE by doubly labeled water (DLW) and physical activity level (PAL) in Japanese patients with diabetes mellitus.

Methods: We planned to recruit sixty patients with type 2 diabetes and sex- and age-matched twenty nondiabetic subjects as the CLEVER-DM Study at a single university hospital. The current presentation is a part of this study with forty-one patients with type 2 diabetes (DM, 69.9 years, men/women: 23/18) and nine patients without DM (non-DM, 67.2 years, men/women: 2/7). TEE was measured over 14 days by DLW method and PAL was calculated as TEE divided by resting energy expenditure assessed by indirect calorimetry.

Results: The numbers of DM patients treated with insulin, oral hypoglycemic agents, and diet/exercise were 13 (31.7%), 20 (48.8%), and 8 (19.5%), respectively. Mean (standard deviation) level of HbA1c was 6.9 (0.8%) for DM and 5.5 (0.4%) for non-DM (p<0.001). Mean (SD) body mass index was 23.2 (2.9) kg/m² for DM and 23.1 (1.9) kg/m² for non-DM. After adjusted for age, sex, fat-free mass, and fat mass, mean TEE was 2150 kcal/day for DM, and 2087 kcal/day for non-DM, and there was no significant difference between two groups, although DM tended to have a higher value (mean difference: 83 kcal/day, 95% confidential interval [CI] -101 to 267 kcal/day). Mean PAL adjusted for sex and age was 1.68 for DM and 1.83 for non-DM, showing no statistical differences (mean difference: 0.04, 95% CI: -0.07 to 0.15).

Conclusion: TEE was comparable between DM and non-DM groups among Japanese.

Supported By: Japan Agency for Medical Research and Development
Effect of Fiber Intake on Glycemia, Insulin Secretion, and Inflammation in Patients with Type 2 Diabetes

CHI TANG, HUSSAM GHANIM, KELLY GREEN, ANTOINE MAKIDISSI, MANAV BATRA, AJAY CHAUDHURI, PARESH DANDONA, Ansonia, CT, Buffalo, NY; Wil- liamsville, NY

Hypothesis. In view of the reduction in post prandial glucose concentrations and the increase in insulin concentrations and the inhibition of post prandial endotoxemia and increases in TLR-4 and TLR-2 expression following the intake of fiber with a high fat high calorie meal (HFHC) in normal subjects, we hypothesized that a similar effect would be observed following the intake with such a meal in patients with type 2 diabetes.

Methods: Ten patients with type 2 diabetes were included in the study and were administered the HFHC meal alone on one day and with dietary fiber (25g of mainly insoluble fiber) a week later. Fasting premeal and post meal samples were obtained sequentially at hourly intervals for 5 hours. Blood samples were processed for preparation of peripheral blood mono-nuclear cells (MNC), plasma and serum.

Results: Post meal glucose concentrations were not altered significantly but the peak increase in post meal insulin concentrations was greater after fiber (39±8 vs. 25±4U/ml, p<0.01) as well as the area under curve (AUC₀₋₅h) (32.4±733 vs. 221.4±464U*₅h*ml⁻¹, p<0.01). Fiber intake also induced an early peak of GLP-1 within 15 minutes (22±15% over baseline, NS) which was missing without fiber. Reactive oxygen species (ROS) generation and NFκB binding by MNC was significantly suppressed after fiber by 32±11% and 38±13%, respectively (p<0.01), as was the magnitude of endotoxinemia AUC₀₋₅h, by 23±8% (p<0.05). In addition, the increase in the expression of TLR-4 and TLR-2 was also suppressed by 42±15% and 36±14%, respectively (p<0.05).

Conclusions. The intake of fiber resulted in an early peak of GLP-1 and a greater increase in insulin concentrations but the increase in glucose was not altered. Fiber intake also suppressed ROS generation and NFκB binding while reducing the magnitude of endotoxemia and the receptor to endotoxin. Thus, the intake of fiber increases insulinogenesis and reduces oxidative and inflammatory stress in patients with type 2 diabetes.

Carnosine Supplementation Improves Serum Resistin Concentrations in Overweight or Obese but Otherwise Healthy Sedentary Adults—Results From Randomised Controlled Trial

BARBORA DE COURTEN, JOZEF UKROPEC, AYA MOUSA, BARBARA UKROPCOVA, GIANCARLO ALDINI, ESTIFANOS BAYE, Clayton, Australia; Bratislava, Slovakia; Melbourne, Australia; Milan, Italy

Adipokines play an important role in the regulation of glucose metabolism. We have previously shown that carnosine supplementation in overweight or obese non-diabetic individuals improved glucose metabolism but did not change adiponectin levels, however its effect on other adipokines has not been investigated. We aimed to determine the effect of carnosine supplementation on serum adipin, resistin and leptin concentrations in these individuals. Twenty-two overweight or obese otherwise healthy adults were randomly assigned to receive either 2g of carnosine (n=13) or identical looking placebo (n=9) for 12 weeks. Serum adipin, leptin and resistin were analysed using a bead-based multiplex assay (LEGENDIPlex™, BioLegend, CA). Carnosine supplementation decreased serum resistin concentrations compared to placebo (mean change from baseline: -35 ± 83 carnosine vs. 35 ± 55 ng/ml placebo, p<0.04). There was a trend for a reduction in serum resistin concentrations after carnosine supplementation (-76 ± 165 ng/ml vs. 35 ± 55 ng/ml placebo, p=0.04). There was a trend for a reduction in serum adipokine concentrations, however its effect on other adipokines has not been investigated. Our findings suggest that carnosine supplementation has an effect on iron parameters in overweight and obese, otherwise healthy adults. We included twenty-six participants, which were randomly allocated to receive 1g carnosine (n=14) or identical placebo (n=12) twice daily for 12 weeks. Iron parameters including iron, ferritin, transferrin, soluble transferrin receptor, total iron binding capacity and iron saturation were measured in serum or plasma by standard commercial assays (Beckman Coulter Diagnostics, New South Wales, Australia). Carnosine supplementation decreased plasma soluble transferrin receptor compared to placebo (mean change difference: -0.07 ± 0.008 mg/l, p = 0.04). None of the other iron parameters were different between carnosine and placebo groups. Soluble transferrin receptor was inversely associated with urinary carnosine concentrations after adjusting for age, sex and body mass index (β coefficient: -0.01; 95% confidence interval: -0.02 to -0.003). Neither carnosine-1 activity nor content correlated with soluble transferrin receptor. Our findings suggest that carnosine may regulate iron metabolism in high risk groups that may contribute to the prevention of insulin resistance and type 2 diabetes. Larger human clinical trials are required to confirm our results.

Supported By: Slovak Academy of Sciences (VEGA 2/191/19); Slovak Research and Development Agency (SRDA 15/0253); Royal Australasian College of Physicians; Diabetes Australia Research Trust; Foundation for High Blood Pressure Research of Australia; Flamma SpA, Italy; Monash University (to E.B.); National Heart Foundation (100884 to B.D.C.)

Correlations between Serum 25-Hydroxyvitamin D and Pancreatic Islet Function in Type 2 Diabetics

NAN LI, MING CHEN, JIAO DONG, SHAOJING YANG, LU XU, YANRUI WANG, HANG SUN, HONG LI, SHEN QI, Shanghai, China

Objective. The relation between type 2 diabetes mellitus (T2DM) and serum-25-hydroxyvitamin D (25(OH)D) is unclear. We aimed to explore the association of 25(OH)D with islet β cell function and insulin resistance in patients with T2DM.

Methods: A total of 466 patients with T2DM and 364 healthy people in our hospital from 2016 to 2018 were enrolled. The difference of 25(OH)D between T2DM group and non-DM group was compared. Patients with T2DM were divided into low 25(OH)D group (LVD group, <47.7nmol/l, n=326) and normal 25(OH)D group (NVD group, >47.7nmol/l, n=140). The correlation between fasting plasma glucose (FPG), fasting insulin (FINS), fasting c-peptide (FCP), glycosylated hemoglobin (HbAlc), HOMA-IR, HOMA-β and 25(OH)D were compared.

Results: Serum level of 25(OH)D in T2DM group was significantly lower than non-DM group (23.3±13.99 vs.69.1±10.78, P<0.001). Levels of FPG, FINS, FCP, HbAlc, HOMA-IR, and HOMA-β in LVD group were higher than NVD group, but there was no significant difference. Correlative analysis showed that there was negative correlation between 25(OH)D and FCP (r=-0.101, P=0.03), but there was no significant correlation with FPG, FINS, HbAlc, HOMA-IR and HOMA-β (r=-0.87, 0.043, -0.290, 0.035, 0.017, all P>0.05). The 25(OH)D of Duration ≥5 years was lower than the Duration < 5 years (42.3±13.98 vs. 42.4±13.45, P=0.964). The 25(OH)D of HbAlc ≥7% was lower than HbAlc < 7% (42.9±13.85 vs. 44.1±13.50, P=0.192). The 25(OH)D in microvascular group was lower than non-microvascular group (40.8±13.82 vs. 43.3±13.72, P=0.059). The 25(OH)D in macrovascular group was higher than non-macrovascular group (42.9±13.95 vs. 42.9±13.23, P=0.007).

Conclusion: The 25(OH)D in patients with T2DM is lower than healthy people and is downregulating with the increase of diabetic duration and HbAlc. There is no defined correlation between 25(OH)D and the pancreatic islet function. The critical significance should be further studied.
780-P

Increase in Galectin-3 Contributes to Glucose Intolerance and Insulin Resistance Following Exposure to the Common Food Additive Carrageenan

JOANNE K. TUBACMAN, SUMIT BHATTACHARYYA, LEONID FEFFERMAN, Chicago, IL

Exposure to low concentration of the common food additive carrageenan (CGN) leads to impaired glucose tolerance and insulin resistance in C57BL/6J mice, due to CGN’s pro-inflammatory effects and changes in phospho-IRS1 phosphorylation. CGN is a sulfated polysaccharide with α1-3 and β1-4 galactosidic bonds. Other studies showed: 1) CGN reduced activity of arylsulfatase B, which removes sulfate groups from N-acetylgalactosamine 4-sulfate residues of chondroitin 4-sulfate (CS) and dermatan sulfate; and 2) galectin-3 binds less with CS when ARSB is reduced. Increase in galectin-3, which binds to β-galactosides, is reported to inhibit insulin signaling (Li et al) by effects on the insulin receptor. This background led to the current assessment of effects of the no-CGN diet on galectin-3 levels in serum and galectin-3 mRNA in circulating mononuclear cells. Blood samples were obtained from adults with prediabetes before and after dietary intervention. Baseline serum galectin-3 values averaged 8.94 ng/ml (range 4.06-12.64). In 7 patients on a no-CGN diet for 12 weeks, the mean level declined to 7.25 ng/ml (p=0.006, paired t-test). In contrast, serum galectin-3 was unchanged in participants on the CGN-containing control diet and increased by over 2 ng/ml in subjects on their regular diet. mRNA expression of galectin-3 (NGAL/S3) in circulating mononuclear cells of patients on the no-CGN diet declined by 69%, and increased by 96% in the CGN-containing diet group and by 98% in the regular diet group (p=0.0002, 1-way ANOVA). Also, serum galectin-3 levels increased to 1.72 times baseline in C57BL/6J mice given CGN in their water supply for 12 weeks. In HepG2 cells, exogenous galectin-3 (25 µg/ml) inhibited insulin-induced glucose uptake by 39%, and was highly correlated with decline in tyrosine phosphorylation of IRS-1. These findings suggest that CGN contributes to glucose intolerance and insulin resistance, in part, by effects on galectin-3.

Supported By: American Diabetes Association (17-16-ICTS-114 to J.K.T.)

781-P

Dietary Energy Density (DED) is Significantly Associated with Obesity in Japanese Patients with Type 2 Diabetes Mellitus (T2DM)

YASUNAGA TAKEDA, KAZUYA FUJIIHARA, SAKIKO Y. MORIKAWA, CHIKA HIRIKAWA, MARIKO HATTAI, DAI ISHI, REIKO HIRASAWA, YOKO YACHI, HIROHITO SONE, Niigata, Japan, Tokushima, Japan, Yamagata, Japan, China, Japan

DED, defined as the ratio of energy intake (EI) to food weight, is receiving increased attention reflecting recent reports of its associations with obesity and T2DM in general populations. However, only a few studies have investigated the associations between DED and metabolic variables in patients with established diabetes, which led us to analyze the association between DED and obesity in Japanese patients with T2DM. Cross-sectionally investigated were 1,576 outpatients with T2DM (men 60.8%) who attended 26 clinics having diabetes specialists. Dietary habits were obtained by the Food Frequency Questionnaire based on food groups (FFQ). DED (kcal/g) was calculated by dividing EI (kcal) from foods (excluding beverages) by these food weights (g) and was categorized into tertiles (low (L), medium (M), high (H), >51.5). We compared nutritional intake between groups by ANOVA. Multivariate logistic regression model was used to estimate adjusted odds ratios for obesity (BMI>30) in each tertile and per 1 kcal/g of DED, together with tests of combined tertiles of DED and EI. Both EI (kcal) (L), 1692; M, 1787; H, 1862, p for trend<0.001) and the fat-energy ratio (%) (L, 28.5; M, 29.5; H, 30.7, p for trend<0.001) were positively associated according to tertiles of DED. Adjusted odds ratios for obesity were also significantly increased according to tertiles of DED (L, ref: M, 1.33(95% CI:1.01-1.75); H, 1.76(1.32-2.36), p for trend<0.001) and 4.29(2.38-7.73) per 1 kcal/g of DED. Possibility of obesity was significantly higher for patients in the top tertile of DED regardless of EI but was not significant for those in the bottom tertile regardless of EI. In conclusion, higher DED, which is related to higher fat intake, was strongly associated with a greater chance of having obesity in T2DM patients regardless of EI. Therefore, DED is critical in assessing diet quality and has clinical relevance in obesity management of patients with T2DM.

782-P

Changes of the Bone Metabolism Markers and Body Composition in Nonalcoholic Fatty Liver Disease by the SGLT2 inhibitor CHIZURO WATANABE, NORIO AKUTA, YOSHIYUKI SUZUKI, MASAHIRO KOYAYASHI, YASUMICHI MURI, HIROMITSU KUMADA, Kanagawa, Japan, Tokyo, Japan

We reported that histological improvement was confirmed after 24 weeks of Canagliflozin (CAN) therapy in nonalcoholic fatty liver disease (NAFLD). While increase of the fracture according to the Canvas Program was reported. In type 2 diabetes patients with NAFLD (T2ND) who showed histological improvement by using CANA (100 mg/ day), we investigated the bone metabolism markers and the body composition (measured using an INBODY770) after at least 1 year of same treatment. The changes of the parameters (Liver enzymes, serum bone specific alkaline phosphatase (BAP), nBMD/mm²) and urinary N-telopeptide of collagen type-I (uNTx: U/l) were investigated before starting treatment (Pre), after 24 weeks (24W), and at the end of follow-up (Post). Six patients (4 men and 2 women, aged 55.3±7.2 years, Hba1c 8.4±2.0%, BMI: 28.6±2.2 and the duration 8.0±7.7 years) were able to evaluate bone metabolism, and the follow-up period was 1.3±0.2 years. Hba1c, Liver enzymes and Ferritin levels showed further improvement after more than 24 weeks. The Post-Pre difference of bone minerals (BMD) showed a significant positive correlation with the change of skeletal muscle mass and a significant negative correlation with Hba1c at 24W. In 2 cases that the rate of skeletal muscle mass loss for total body weight loss at 24W was ≥30%, the Post BMI decreased more than 5%. There was no correlation with the improvement of the NAFLD activity score by the liver biopsy. BAP levels didn’t change during CANA treatment, while uNTx levels increased in all patients at 24W, but almost returned to Pre levels at Post. uNTx: Pre 31.3(8.2)/ 24W 425.9(44.5) S/ Post 38.1(3.8). The uNTx levels showed a pronounced increase from Pre (24.0) to 26W (214.3) in 1 patient with a history of fracture. During long-term CANA therapy, there was ongoing improvement of the liver inflammation markers in 12ND, while these findings suggest that early changes of bone resorption by CANA therapy predict the subsequent state of bone metabolism.

783-P

Excess Nicotinamide Induces Reactive Oxygen Species Generation, Insulin Resistance, and Epigenetic Change in Rats and Humans YAMING ZHOU, NANA CHEN, DA LI, WUPING SUN, SHI-SHENG ZHOU, Boston, MA, Nagoya, Japan Shenyang, China, Shenzhen, China, Dalian, China

The implementation of grain fortification with niacin, commonly in the form of nicotinamide, has significantly increased niacin per capita consumption in U.S. from 1930s. Nicotinamide is the precursor of NAD and NADP, which participate in many biological reactions. Therefore, nicotinamide homeostasis is vitally important for the body. This study is to investigate the effects of excess nicotinamide on ROS generation, insulin resistance, and epigenetic change, which are hallmarks of type 2 diabetes.

We found acute nicotinamide overload increased ROS generation, insulin resistance, and reduced muscle glycogen level in adult rats. Besides these effects, long-term nicotinamide overload led to oxidative stress in kidney and liver, increased their DNA damage, and decreased their global DNA methylation profile. We further demonstrated that decreasing nicotinamide degradation and excretion level was crucial for the ROS generation- and insulin resistance-inducing effects using an impaired skin detoxification rat model.

Using oral glucose tolerance test (OGTT), we observed that in healthy volunteers, nicotinamide addition induced higher levels of ROS generation and insulin resistance in the early phase, followed by hypoglycemia in the late phase. Compared to controls, diabetic patients showed a disturbed nicotinamide degradation pattern, characterized by higher plasma N-methylnicotinamide (NMA) levels and lower urinary degraded metabolite, N'-methyl-2-pyridone-5-carboxamide (2-Py).

Mechanistically nicotinamide degradation process was associated with ROS generation; excess nicotinamide led to higher ROS generation causing kidney and liver damage. We also found that excess nicotinamide disturbed the monoamine neurotransmitters degradation and DNA methylation by competing for the biological methyl-donor, betaine in the body.

In summary, our results indicate that excess nicotinamide may play an important role in type 2 diabetes.

Supported By: National Natural Science Foundation of China
The Effect of Two Isocaloric and Energy-Matched Plant-Based and Processed-Meat Meals on Glycose Metabolism, Gastrointestinal Hormones, and Satiety in Subjects with T2D, Obese Subjects, and Healthy Controls—A Randomized Crossover Study

MARTA MENTOVA, LENKA BÉLOVÁ, MARTIN HÁLEK, RENATA PAVLOVÁ, MARTIN HILL, TEREZIE PELIKANOVÁ, HANA KARLEOVA, Prague, Czech Republic, Washington, DC

Objective: Gastrointestinal hormones play a key role in glucose metabolism and energy homeostasis.

Methods: A randomized cross-over study was used to test the effects of two energy- (600 kcal) and macronutrient-matched plant-based and processed-meat meals (41% carbohydrates, 19% protein, and 40% lipids) on glucose metabolism, plasma concentrations of gastrointestinal hormones, and satiety in subjects with T2D (n=20), obese subjects (n=20) and healthy controls (n=20). Plasma concentrations of glucose, immunoreactive insulin, C-peptide, GLP-1, GIP, amylin and PYY, along with satiety, were determined at 0, 30, 60, 120 and 180 min. Repeated-measures ANOVA was used for statistical analysis.

Results: An increase in stimulated secretion of immunoreactive insulin was observed in T2D and obese subjects (p=0.005, and p=0.045, respectively) after the plant-based meal. We observed an increase in stimulated secretion of C-peptide in all groups after the plant-based meal (p<0.001 for T2D, p=0.014 for obese subjects, and p=0.001 for healthy controls). An increase in postprandial concentrations of amylin was observed in T2D and healthy controls after the plant-based meal (p<0.001 for both groups). An increase in stimulated secretion of GLP-1 was observed in T2D obese subjects and healthy controls (p<0.001, and p=0.01, respectively) after the plant-based meal. A decrease in peak concentrations of GIP (at 60 min.), and an increase in peak concentrations of PYY, were observed in all groups after the plant-based meal. The participants in all groups reported greater satiety after the plant-based meal (p=0.004 for T2D, p<0.001 for obese subjects, and p<0.001 for healthy controls).

Conclusions: Our study suggests that plant-based meals may be effective in increasing stimulated secretion of GIP-1, insulin, amylin and PYY, as well as in promoting satiety.

Supported By: Ministry of Health of the Czech Republic (I2V15-273398, 20023001)

Impact of Carbohydrate Intake on Obesity in Japanese Patients with Type 2 Diabetes—An Analysis of the JDCP Registry

SATOMI MATSUNAGA, HIROHITO SONE, KINSUKE TSUDA, YOSHIHARU OSHIDA, SATOSHI SASSAKI, JO SATOH, YASUHIKO HAYASHINO, RIMEI NISHIMURA, NACKO TAJMA, Niigata, Japan, Sakai, Japan, Nagoya, Japan, Tokyo, Japan, Sendai, Japan, Nara, Japan

While the clinical relevance of a low carbohydrate diet for obese patients with diabetes is still a matter of debate, the optimal amount of carbohydrates has not yet been elucidated. Therefore, we investigated the association between obesity and the carbohydrate intake while considering the physical activity (PA) levels in patients with type 2 diabetes. Japanese patients with type 2 diabetes in a nation-wide registry who completed a lifestyle survey, but were not on insulin therapy (N=1111, mean age 61.7 y, mean BMI 24.4 kg/m²) were included in this cross-sectional study. The carbohydrate intake and PA were evaluated by the Brief-type self-administered Diet History Questionnaire and the International Physical Activity Questionnaire, respectively. Participants were stratified into two groups according to whether they were above or below the PA of 1380 MET min/week which is the level recommended by the Japan Diabetes Society and WHOD, as well as into tertiles according to their carbohydrate intake. The odds ratio (OR) for obesity defined as BMI ≥25 kg/m² in each combined category was determined by a multivariate logistic regression model. The main daily intake of energy, carbohydrate, protein, and fat was 1995 kcal, 233g, 63g, and 44g, respectively, and the median PA was 1386 MET min/week. ORs for obesity in participants whose carbohydrate intake was in the top tertile (≥253g/day) and a PA of <1380 MET min/week compared to those whose carbohydrate intake was in the bottom tertile (<196 g/day) and a PA of ≥ 1380 MET min/week were 1.8 (85% CI, 1.2-2.9, p=0.01). However, the association became non-significant when adjusted by energy intake instead of the amount of fat and protein.

In conclusion, a daily carbohydrate intake of more than approx. 250 g was significantly associated with obesity in combination with an inactive state in Japanese patients with type 2 diabetes, even though the energy intake might have as strong impact as carbohydrate intake.

Supported By: Japan Ministry of Health, Labour and Welfare, Japan Diabetes Society

Baseline Vitamin D as a Surrogate Marker for Type 2 Diabetes Remission and Weight Loss following Sleeve Gastrectomy

ALANOU D ALADEL, MILAN K. PIA, SAHAR AZHARIAN, MARK CHRISTIAN, VINOD MENON, PHILIP G. MCTERNAN, Coventry, United Kingdom; Sydney, Australia; Nottingham, United Kingdom

Background: Vitamin D deficiency is associated with obesity and type 2 diabetes mellitus (T2DM), although the use of circulating Vitamin D levels as a predictor of weight loss induced T2DM remission is unclear. Therefore, the aim of this study was to analyze whether pre-bariatric surgery vitamin D levels may predict T2DM outcomes 12 months post-SG.

Methods: A cohort of 220 obese participants (74.5% female) with T2DM (Age: 50±9.5 year, BMI: 51.4±7.9kg/m²; n=103) and without T2DM (Age: 46±9 year, BMI: 53.5±8.5kg/m²; n=117) undergoing SG participated in an ethics approved study in a single bariatric centre in the UK. Patient anthropometric and biochemical data including vitamin D were collected at baseline and 12 months post-SG; no vitamin D supplementation at baseline was given.

Results: Baseline vitamin D levels inversely correlated with baseline BMI (p<0.001, n=0.35). Age, pre-op weight and vitamin D levels were correlated with HbA1c 12 months post-SG (R=0.001, n=0.28; P<0.001, n=0.25 and P<0.05, n=0.19). Furthermore, baseline vitamin D levels predicted levels of HbA1c post-surgery following adjustment for pre-op weight loss and age. Within the T2DM group, those that achieved T2DM remission 12 months post-SG (45.5%, n=51) had a higher baseline Vitamin D compared to those not in remission (43.5±23.8 vs. 33±19ng/mL; p<0.05), with no significant differences between the two groups in baseline BMI, hypertension, pre-op weight loss or excess weight loss (EWL). Interestingly, patients with higher pre-surgical Vitamin D levels also had significantly lower BMI (P<0.005) and higher % EWL (P=0.05) 12 months post-surgery.

Conclusion: Baseline Vitamin D levels appear to be an independent indicator for successful T2DM remission and weight loss, 12 months following SG. The use of baseline Vitamin D levels may help us predict those more likely to do well and prioritize post-surgery support to achieve success for all participant groups.

Supported By: King Saud University

Protein-Restricted Diet Is Effective in Decreasing Glycemia, HbA1c, and Cholesterol in Type 2 Diabetic Subjects by the Activation of the ATF4 (Activating transcription factor 4) and CHOP (C/EBP homologous protein) Pathway

RAFAEL C. FERRAZ, REBECA A. BERALDO, PATRICIA GOMES, MILTON C. FOSS, MARIA CRISTINA FOSS FREITAS, Ribeirão Preto, Brazil

Dietary restriction increases lifespan across the evolutionary spectrum and decreases metabolic disease risk in mammals. It has been shown that amino acid restriction is sufficient to promote some of the beneficial effects of dietary restriction in rodents. This phenomenon is dependent on GCN2 (general control non-essential 2), a kinase activated by amino acid restriction that controls protein synthesis and stress response. Our results show that treatment of type 2 diabetic subjects on a protein restriction diet for 4 weeks exhibited a 61% reduction in fasting glucose levels and a 14% decrease in HbA1c. These patients had a 2% reduction in total cholesterol with a 33% decrease in LDL. We noticed a reduction of 4.5% of body weight, with a decrease of 11% of fat mass and maintenance of lean mass. In addition, all subjects had systemic blood pressure normalization, with a decrease of 11% of fat mass and maintenance of lean mass.

Conclusion: Our study suggests that protein restricted diet may be effective in improving stimulated secretion of GIP-1, insulin, amylin and PYY, as well as in promoting satiety.

Supported By: Fundação de Amparo à Pesquisa do Estado de São Paulo

Impact of Carbohydrate Intake on Obesity in Japanese Patients with Type 2 Diabetes—An Analysis of the JDCP Registry

While the clinical relevance of a low carbohydrate diet for obese patients with diabetes is still a matter of debate, the optimal amount of carbohydrates has not yet been elucidated. Therefore, we investigated the association between obesity and the carbohydrate intake while considering the physical activity (PA) levels in patients with type 2 diabetes. Japanese patients with type 2 diabetes in a nation-wide registry who completed a lifestyle survey, but were not on insulin therapy (N=1111, mean age 61.7 y, mean BMI 24.4 kg/m²) were included in this cross-sectional study. The carbohydrate intake and PA were evaluated by the Brief-type self-administered Diet History Questionnaire and the International Physical Activity Questionnaire, respectively. Participants were stratified into two groups according to whether they were above or below the PA of 1380 MET min/week which is the level recommended by the Japan Diabetes Society and WHOD, as well as into tertiles according to their carbohydrate intake. The odds ratio (OR) for obesity defined as BMI ≥25 kg/m² in each combined category was determined by a multivariate logistic regression model. The mean daily intake of energy, carbohydrate, protein, and fat was 1995 kcal, 233g, 63g, and 44g, respectively, and the median PA was 1386 MET min/week. ORs for obesity in participants whose carbohydrate intake was in the top tertile (≥253g/day) and a PA of <1380 MET min/week compared to those whose carbohydrate intake was in the bottom tertile (<196 g/day) and a PA of ≥ 1380 MET min/week were 1.8 (85% CI, 1.2-2.9, p=0.01). However, the association became non-significant when adjusted by energy intake instead of the amount of fat and protein.

In conclusion, a daily carbohydrate intake of more than approx. 250 g was significantly associated with obesity in combination with an inactive state in Japanese patients with type 2 diabetes, even though the energy intake might have as strong impact as carbohydrate intake.

Supported By: Japan Ministry of Health, Labour and Welfare, Japan Diabetes Society
Ascorbic Acid Supplementation Improves Postprandial Glucose and Blood Pressure in People with Type 2 Diabetes

SHAUN MASON, BIDIL RASMUSSEN, GLENN D. WADLEY, Melbourne, Australia, Burwood, Australia

The aim of the study was to investigate whether ascorbic acid (AA) supplementation improves postprandial glucose responses under free living conditions in people with type 2 diabetes (T2D). Thirty-one people with T2D (26 male, 5 female; aged 61.8 ± 6.8 years; duration of diabetes 5.6 ± 4.6 years [mean ± SD]) and stable glucose control (HbA1c 7.6 ± 0.7%) and blood pressure (SBP 139 ± 10, DBP 85 ± 9 mmHg) completed a randomized cross-over study involving 4 months of oral AA (2 x 500 mg/day) supplementation and 4 months of placebo supplementation (# ACTRN12616000276459). A minimum wash-out of 4 weeks separated treatments. Participants were affixed with continuous glucose monitors for 48 hours and consumed standardized meals pre and post supplementation. Intention to treat analyses were used to analyse data. Postprandial glucose area under the curve for 3.5 hours post meals (10.5 hours total) and the percent of day spent in hypoglycaemia (>10 mmol/l) were significantly lower by 31% and 11% (~2.5 hours) after AA supplementation when compared to placebo, respectively (p<0.05). Significantly lower systolic (-6 mmHg) and diastolic (-4 mmHg) blood pressures were also found after AA supplementation compared to placebo. There were no effects of AA supplementation on percent of day spent in hyperglycaemia (<4 mmol/l), average 24 hour glucose or HbA1c. Treatments were well tolerated by participants, with no adverse effects reported. Capsule compliance was high for both treatments (AA: 93 ± 11%, placebo: 95 ± 7%).

In summary, AA supplementation attenuated the daily post-prandial glucose response and the proportion of day spent in hyperglycaemia in people with T2D. AA also improved blood pressure in this group. This evidence collected under free-living conditions strengthens the argument for AA as a beneficial adjunct therapy to improve glycaemic control and cardio-metabolic health for people with T2D.

Supported By: Diabetes Australia

Effect of Stevia on Glycemic and Insulin Responses in Obese Patients—A Randomized, Double-Blind, Placebo-Controlled Cross-over Study

PARINYA SAMAKKARINTHAI, MANAPORN PAYANUNDANA, NATTAPOL SATHAVARodom, CHONPITI SIRIWAN, APUSANee BOONYVARAKUL, Bangkok, Thailand

Background: Stevia is natural nonnutritive sweeteners (NNS) that is considered to be metabolic inert in contrast with artificial NNS, especially sucralose, which cause glucose intolerance in obese patients. However, acute effect of stevia ingestion on glycemic and insulin responses in obese patients are not clearly established.

Objectives: To assess acute effect of stevia on glycemic and insulin responses in obese patients.

Material and Methods: Obese patients underwent a 75-gm oral glucose tolerance test (OGTT) preceded by consuming pills containing either 200 mg stevia or placebo for 60 minutes before test on two separate occasions, 1 week apart, in a randomized crossover design. Blood samples were obtained for glucose and insulin at 0,30,60,90 and 120 minutes. Area under the curve (AUC) of glucose and insulin responses were calculated. Indices for insulin sensitivity (Matsuda index) and insulin secretion (Insulinogenic index) were calculated using minimal models of glucose and insulin kinetics.

Results: Twenty obese patients (BMI 28.7±3.68 kg/m²) were recruited to the study. There were no significant differences in AUC of glucose and insulin between stevia and placebo (glucose, 15,285±4,531 vs. 15,101 ±3,955, p=0.89 and insulin 8,507 ±5,858 vs. 7,652 ± 5,020, p=0.62) Insulin sensitivity derived from OGTT using Matsuda index was not significant difference between stevia and placebo (4.74±1.96 vs. 5.84±2.96, p=0.09). Insulin secretion using Insulinogenic index was not significant difference between stevia and placebo (p=0.155).

Conclusions: Stevia does not affect in acute glycemic and insulin responses to OGTT in obese patients. This findings need to be determined in longer duration of ingestion study.

Supported By: Endocrine Society of Thailand

Effect of a Novel Ficus Carica (Fig) Fruit Extract Standardized in Abscisic Acid on the Glycemic and Insulinemic Responses in Healthy Human Subjects

ANDREA ZANGARA, Moller del Villar, Spain

Abscisic acid (ABA) is a phyto-hormone present in different fruits and has important implications for human health, such as glucose homeostasis, increase of glucose tolerance, insulinemia attenuation, immune and anti-inflammatory functions. Fig extracts represent an important source of ABA and have therefore the potential to provide a natural balance for sugar and insulin control. The objective of this study was to determine the acute postprandial metabolic response on glycemia and insulinemia of standardized fig extracts (ABAlife™). Healthy subjects (n=10) consumed a glucose solution and a fig extract at two different concentrations Reference food: Glucose solution (50 g) in 250 mL of water. Test food 1: Glucose solution + 200 mg ABAlife (80 µg ABA) in 250 mL of water. Test food 2: Glucose solution + 100 mg ABAlife (40 µg ABA) in 250 mL of water. The results showed that the addition of ABAlife extracts to a glucose solution was able to reduce considerably both the glycemic index (GI) and insulinemic index (II) values. Fig Extract (100-200 mg) produced lower peak and overall glycemic and insulinemic responses, between 30-120 minutes, compared with reference food of glucose. The supplementation of Fig Extract (200 mg) to a glucose solution was able to produce considerable reductions of the GI and II values (25%, p<0.001 and 24%, p<0.05, respectively). Moreover, a dose response reduction of II was observed with both ABAlife extracts. Therefore, small amounts of ABA from ABAlife extracts could be proposed as an interesting strategy to reduce postprandial glucose and insulin responses and ABA potential to manage glucose metabolism disorders should be investigated in further chronic clinical trials.

Effect of Resistant Starch on Postprandial Glucose Levels in Sedentary, Abdominally Obese Persons

TONGYU MA, CHING-DO LEE, Phoenix, AZ

Background: Although the resistant starch (RS) supplementation has shown promise in lowering postprandial glucose in healthy non-obese persons, little is known about the effect of RS on postprandial glucose levels in abdominally obese persons.

Supported By: ADA-Supported Research
Objective: This study examined the effect of RS-supplemented muffins on postprandial glucose levels in sedentary, abdominally obese individuals as compared with digestible carbohydrates-matched oral glucose solution.

Method: A total of 8 sedentary, abdominally obese participants were randomly assigned to two sequences of treatments (AB, BA) using a 2 x 2 randomized cross-over design. The treatment effect tested with a muffin that contained 75 g of digestible carbohydrates and 30 g of RS (TRT), with the control tested using a 75-g oral glucose solution as a control condition (CON). Linear mixed models were used to test the treatment effect (TRT vs. CON) on glucose values and area under the curve (AUC).

Results: The 2-h postprandial glucose AUC was significantly lower in the TRT than in the CON (12.5±1.6 mmol/L vs. 15.6±3.3 mmol/L, P=0.002). The glucose levels were also significantly lower in the TRT than in the CON at 30 minutes (6.6±0.8 vs. 8.3±1.3 mmol/L, P=0.001), 60 minutes (6.5±1.1 vs. 8.5±2.1 mmol/L, P=0.004), and 90 minutes (6.3±1.1 vs. 8.1±1.8 mmol/L, P=0.003). The 2-h postprandial insulin AUC was also significantly lower in the TRT than in the CON (1354.5±606 vs. 1788.9±522.8 pmol/L·h, P=0.001). Based on the 2-h glucose incremental AUC values, the calculated glycaemic index of the RS-supplemented muffins was 48 (glucose=100).

Conclusion: The RS muffins supplemented with 30 g of RS could reduce postprandial glucose and insulin responses in abdominally obese adults.

Supported By: Arizona State University

793-P

Contribution of Eating Behaviours to Glucose Dysmetabolism

SIMONA RATTI, ALESSANDRO LEGONE, RAMONA DE AMICIS, ALBERTO BATEZATI, Piazzera, Italy, Milan, Italy

The contribution of eating behaviors (EBs) and their psychological constructs to glucose dysmetabolism is still debated. To investigate this issue we conducted a cross-sectional study on 4095 subjects seeking a weight loss program, (71% females and 29% of subjects overweight or obese). Serum glucose and insulin were measured, and HOMA (HI) index was calculated. Impaired fasting glucose (IFG) was defined as a serum glucose ≥100 mg/dL. EBs were investigated using the Binge Eating Scale (BES) and the Eating Disorder Inventory 3 (EDI3). Raw scores for binge eating behavior (BE) bulimia (B), drive for thickness (DT) and body dissatisfaction (BD) were calculated. Multivariable linear and logistic regression models, adjusted for sex, age, BMI, smoking and physical activity were used to assess the association of BES and EDI3 with serum glucose, HI and the risk of IFG, respectively. BES score and EDI3 scales were not associated with serum glucose and HI, whereas DT ≥0.1 mg/dL, CI 95%: -0.17 to -0.04; for 1-point increment in DT scale) and BD ≥0.18 mg/dL, CI95%: -0.24 to -0.12; for 1-point increment in BD scale) scales were slightly and inversely associated with serum glucose, BE, B and DT were not associated with IFG. Only subjects experiencing BD had a lower risk of IFG (OR=0.72, CI95%:0.61,0.85).

In conclusion, given the very small effect size, BE, B and DT do not seem to contribute in biologically meaningful manner with glucose profile and IFG risk, whereas BD is associated with a lower risk of IFG. Further study to investigate the effect of BD on food habits and dietary pattern are needed to better understand the contribution of psychological constructs of EBs on glucose dysmetabolism.
Behavioral Medicine, Clinical Nutrition, Education, and Exercise

POSTERS

High Prevalence of Distress among Patients with Type 2 Diabetes (T2DM)—A Hospital-Based, Cross-Sectional Study from South India

PRASANThi SANKAR, PRIYANKA SASIKUMAR, RITUJNA MEADvIl, RITTIN JACOB, SARANYA SASIDHARAN, Pathanamthitta, India

Background: Diabetes distress (DD) refers to unique, often hidden emotional burdens and worries associated with the diabetes experience. DD is common, is distinct from depression, and has been associated with glycemnic level and disease management. T1-REDEEM (Type 1:Reducing Distress and Enhancing Effective Management) was an RCT that compared two interventions to reduce DD among adults with type 1 diabetes (T1D). After baseline assessment, participants were randomized to either KnowIt, a diabetes education and management program, or OnTrack, which focused on recognizing, normalizing and addressing DD. Both programs involved a 1-day group workshop followed by four 1-hour online group meetings over 3 months. Recruitment occurred at clinic and community sites in three Western U.S. states and Toronto, Canada. Inclusion criteria were T1D ≥ 12 months, elevated DD (> 2.0 on the Diabetes Distress Scale), age ≥ 21 years, HbA1C ≥ 7.5% (58 mmol/mol), and English speaking. Regression models analyzed change in DD and HbA1C at 3 months (p=0.05) that did not differ by group. Findings suggest that effective interventions to address DD must focus on the emotional side of diabetes, especially for participants with high DD, poor emotion regulation, poorer problem-solving skills, and higher knowledge at baseline. KnowIt led to significantly greater DD reductions for those with lower diabetes knowledge at baseline. There was a modest decrease in HbA1C at 3 months (p = 0.05) that did not differ by group. Findings suggest that effective interventions to address DD must focus on the emotional side of diabetes, especially for participants with high DD, poor emotion regulation, poorer problem-solving skills, and different levels of diabetes knowledge.

Supported By: National Institutes of Health (DK094863)

Supported By: Manpezi Suzuki Diabetes Foundation; Japan Society for the Promotion of Science (25486841)

Moderated Poster Discussion: Interventions and Outcomes of Behavioral and Psychosocial Factors in Diabetes (Posters: 800-P to 805-F, see page 12)

Behavior Change of Participants in Group vs. Individual DPP Weight Loss Interventions—The SHINE Study

PAULa M. TRIF, LINDA M. DELAHANTY, DONALD A. CIBULa, RUTH S. WEINSTOCK, Syracuse, NY; Boston, MA

Objective: To compare change in physical activity (PA) and dietary fat intake (DFI) in the SHINE (Support, Health Information, Nutrition and Exercise) Study. SHINE was a randomized, controlled weight loss trial (n=257) of 2 telephone (to increase reach) translations of the Diabetes Prevention Program (DPP) lifestyle change intervention, delivered at 5 diverse healthcare sites.

Methods: Participants (metabolic syndrome, no diabetes) were randomized to the DPP lifestyle change program, participating individually (solo;
The purpose of the study was to examine the effect of Motivational Interviewing to Improve Insulin Acceptance in insulin naïve patients with type 2 diabetes. Participants were recruited from outpatient clinics in two academic affiliated hospitals in South Korea. A matched subjects design was used to allocate the intervention (n=55) and control (n=55) groups based on age, gender, and the stage of intention to receive insulin therapy. The stages of intention to receive insulin were previously reported that both group and solo arms lost significant weight, but solo participants regained. Here we look at change in PA (International Physical Activity Quest.) and DFI (NCI Fat Screener). Mixed linear models compared mean change from baseline in PA and DFI, within and between arms, at 6, 12 and 24 mos. for this longitudinal dataset. Results: Compared to baseline, the group arm increased PA at 6, 12 and 24 mos. (71.0, 139.5, 255.0 mets/week), the solo arm only improved at 24 mos. (102.0 mets/week). Compared to baseline, the group arm showed decreased DFI at 6, 12 and 24 mos. (1.4%, 1.4%, 1.4%), the solo arm improved at 6 and 12 mos. (2%, 2.9%) but not at 24 mos. There were no differences between arms in means for PA or DFI.

Conclusions: Primary care staff can be trained to deliver a telethonic DPP translation that is effective to achieve significant PA and DFI behavior change. Despite anecdotal concerns that group contact may be less tailored to individuals and thus less effective, we found that group may be more effective than solo contact in achieving activity and diet changes associated with weight loss.

Supported By: National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases
was a prospective randomized controlled trial that evaluated the effectiveness of a 16-session severity tailored cognitive behavioral intervention plus lifestyle change counseling (n = 67, IG=intervention group) delivered by trained staff compared to usual care (n = 72, CG=control group), in 139 rural adult patients (mean age = 52.6 ± 9.5 years, 72% black; BMI = 37.0 ± 9.0). With uncontrolled mean A1c = 9.8 ± 2.0 type 2 diabetes and co-morbid depressive (PHQ-2) or distress (DDS-2) symptoms at screening in an academic primary care clinic. At baseline and at 12-month follow-up: A1c, RRD (sub-score of DDS-17), self-care behaviors (SDSCA), and medication adherence (Medication Adherence Questionnaire (Medication Adherence Questionnaire)) were measured using validated instruments. This analysis specifically examined changes in RRD in insulin users (n = 41, 61%) vs. oral medications and lifestyle change users (n = 26, 39%) in the intervention arm only. While A1c was higher in insulin users at baseline as expected, there were no other significant differences between insulin-users and non-users at baseline. Cognitive behavioral intervention produced comparable improvement in RRD (1.1 ± 1.3 vs. -1.0 ± 0.9, p = 0.6), self-care behaviors (1.0 ± 1.3 vs. +1.3 ± 1.3; p = 0.4) and medication adherence (1.0 ± 1.9 vs. +1.0 ± 2.2; p = 0.9) in insulin users vs. non-users. Insulin users had a greater reduction in A1c (-1.1 ± 1.9 vs. -0.6 ± 1.5, p = 0.3). Tailored cognitive behavioral intervention produces comparable improvements in RRD, self-care behaviors, medication adherence and A1c in insulin users and non-users.

Supported By: Bristol-Myers Squibb Foundation

Ketones to Success—Does NICH Involvement Influence DKA Discharge Presentation?

DAVID V. WAGNER, ROSE CHUONG, NATALIE C. KOSKELA, HANNAH LUZOD, ERYNN BEESON, INES GUTTMANN-BAUMAN, MICHAEL A. HARRIS, Portland, OR

Objective: Youth with diabetes and medical management are at increased risk of DKA. Novel Interventions in Children’s Healthcare (NICH) is designed to reduce the risk of young people who are experiencing or are at high risk of experiencing DKA. Previous findings from smaller samples indicate that youth in NICH are less likely to experience a DKA event and typically experience a shorter average hospital stay. However, counter to physician anecdotes, DKA-related lab values at admission for NICH patients do not differ from labs prior to program involvement. This study aims to determine whether patients in NICH are being discharged when less stable.

Methods: Retrospective chart reviews were conducted on 52 youth enrolled and treated with NICH. Data included presence and number of DKA episodes in the year prior to and the year following NICH enrollment, as well as associated lab values at discharge—ketones, blood glucose level, bicarb, and pH. The mean age youth was 14.7 years (SD=3.5); 55.8% were female; and 92.3% were Caucasian. Eighteen youth had lab values associated with DKA discharge available both prior to and during NICH.

Results: Youth were less likely (p=.001) to experience DKA during NICH (M=1.0; SD=1.8) than prior (M=1.8; SD=2.1). DKA discharge was less likely (t(51)=3.53; p=.001) during NICH (M=1.0; SD=1.8) than prior (M=1.8; SD=2.1). Ketones to Success—Does NICH Involvement Influence DKA Discharge Presentation?

DAVID V. WAGNER, ROSE CHUONG, NATALIE C. KOSKELA, HANNAH LUZOD, ERYNN BEESON, INES GUTTMANN-BAUMAN, MICHAEL A. HARRIS, Portland, OR

Objective: Youth with diabetes and medical management are at increased risk of DKA. Novel Interventions in Children’s Healthcare (NICH) is designed to reduce the risk of young people who are experiencing or are at high risk of experiencing DKA. Previous findings from smaller samples indicate that youth in NICH are less likely to experience a DKA event and typically experience a shorter average hospital stay. However, counter to physician anecdotes, DKA-related lab values at admission for NICH patients do not differ from labs prior to program involvement. This study aims to determine whether patients in NICH are being discharged when less stable.

Methods: Retrospective chart reviews were conducted on 52 youth enrolled and treated with NICH. Data included presence and number of DKA episodes in the year prior to and the year following NICH enrollment, as well as associated lab values at discharge—ketones, blood glucose level, bicarb, and pH. The mean age youth was 14.7 years (SD=3.5); 55.8% were female; and 92.3% were Caucasian. Eighteen youth had lab values associated with DKA discharge available both prior to and during NICH.

Results: Youth were less likely (p=.001) to experience DKA during NICH (M=1.0; SD=1.8) than prior (M=1.8; SD=2.1). DKA discharge was less likely (t(51)=3.53; p=.001) during NICH (M=1.0; SD=1.8) than prior (M=1.8; SD=2.1). Regarding discharge presentation, only the presence of ketones indicated a significant difference (t(72)=2.21; p<0.05), with patients in NICH being discharged with trace to small ketones on average while in the program, as opposed to negative to trace ketones prior to program involvement.

Conclusions: Youth in NICH experience fewer DKA events and are less likely to experience a DKA during program involvement. In addition, youth are discharged, on average, with a stronger presence of ketones during NICH than prior to program involvement. This may reflect increased medical provider confidence that ketones and associated youth health can be managed at home when NICH providers are involved.

Factors Affecting Noninsulin Antidiabetic Drug Adherence in Patients with Type 2 Diabetes

LINDSAY PETRENCHIK, F. ELLEN LOH, New York, NY

Adherence to antidiabetic (AD) medication is a multifactorial phenomenon; however, little is known about which factors are the most contributory. Our objective was to conduct a systematic review aiming to quantify the effect of factors associated with medication nonadherence in patients with type 2 diabetes using noninsulin AD (NIAD) drugs. We conducted a systematic literature search of relevant observational studies published from January 1997 through March 2017. Studies were included if they used medication possession ratio (MPR) or proportion of days covered (PDC) to evaluate adherence associated with factors, were published in the last 10 years, and did not include insulin. The factors identified were then grouped based on the dimensions of medication adherence defined by the World Health Organization (WHO). The search yielded 106 studies of which 25 met criteria. Socioeconomic factors associated with increased adherence were older age, male gender, and caucasian race which were supported by 15, 10, and 8 studies, respectively. Health system related-factors associated with increased adherence were a general practitioner as the initial prescriber and mailed prescriptions, which were supported by 2 and 3 studies, respectively. The most prevalent condition-related factors were no hospitalization in the past year, frequent physician visits, and absence of cancer, each of which were supported by 2 studies. In regards to therapy-related factors, patients prescribed metformin, and who have a higher pill burden are more likely to be adherent, which were supported by 5 and 8 studies respectively. Only one study analyzed a WHO defined patient-related factor, which found a negative relationship between patients’ diabetes-related knowledge and adherence.

In conclusion, the major factors reported to be associated with NIAD nonadherence were younger age, female, non-caucasian race, not using mailed prescriptions, cancer diagnosis, lower number of comorbidities, and a smaller pill burden.

Engaging Hispanic Adolescents with Type 2 Diabetes or Obesity in Personalized Exercise

MELISSA S. FAULKNER, SARA MICHALISZYN, Atlanta, GA, Youngstown, OH

The prevalence of obesity in Hispanic youth (21.9%, Ogden and Flegal, 2015) is the highest of all racial and ethnic groups, increasing their odds for the development of type 2 diabetes (T2D). The purpose of this secondary analysis of a larger trial of a 16-week personalized exercise intervention was to examine differences in exercise adherence and baseline perceptions of benefits and barriers to exercise, exercise self-efficacy and family support in exercise to Hispanic adolescents diagnosed with T2D or obesity. Changes in body mass index, waist circumference, glycosylated hemoglobin (HbA1c), homeostatic model for insulin resistance (HOMA-IR), lipid profile, cardiopulmonary fitness, blood pressure and perception of health were also examined following the intervention. There were 21 adolescents enrolled in the study, 13 with T2D (3 males, 10 females) and 8 who were obese (3 males, 5 females). The personalized programs were based upon individual adolescent choices to promote moderate to vigorous activity (MVPA) and included gym memberships, dance videos, biking, basketball, softball and walking. Adolescents wore the Actigraph® accelerometer (model GT1M, Pensacola, FL) for tracking exercise throughout the intervention. The completion rate was 88% vs. 56% (71% overall) for obese vs. T2D, with obese adolescents engaging in higher duration of MVPA compared to those with T2D (mean 46.4 ± 33.8 vs. 36.3 ± 16.0 min/day). Perceptions of family support for exercise were associated with benefits of exercise (r = .50, p = .021); barriers to exercise were associated with less MVPA (r = -.56, p = .017). Barriers were significantly higher in those with T2D (p = .01). Despite not meeting recommended activity guidelines, perceptions of health improved for all completing the intervention (p = .01). Future efforts for engaging Hispanic adolescents in regular exercise are warranted to delay the onset of T2D and the development of poor outcomes particularly for those already diagnosed with T2D.

Supported By: National Institutes of Health (R21NR009267)

Clinical Relevance of the Behavioral Stages of Change with the Efficacy of Multifaceted Interventions on the Drop-Out from Regular Medical Care in Patients with Diabetes—The Japan Diabetes Outcome Intervention Trial-2 (J-DOTIT2)

RYOTARO BOUCHI, MITSUHIKO NODA, YASUAKI HAYASHINO, KATSUYA YAMAZAKI, HIKARI SUZUKI, ATSUSHI GOTO, TOUSHI A. FURUKAWA, KAZUO IZUMI, MASASHI KOYABASHI, J-DOTIT2 STUDY GROUP, Tokyo, Japan, Saitama, Japan, Nara, Japan, Saitama, Japan, Nara, Japan, Tokyo, Japan, Kyoto, Japan

Background: To examine the impact of lifestyle intervention by telephone (TSC) and face-to-face (FFA) according to the stages of lifestyle change (SLC) on the drop-out from regular medical care of diabetes.

Methods: Secondary analysis was performed on data from the Japan Diabetes Outcome Intervention Trial-2 large trial (J-DOTIT2-LT), which was a 1-year, prospective, cluster randomized, intervention trial. 11 district medical associations were divided into two subregions (clusters), in which patients were registered, and then were randomized to an intervention group (TSC or FFA) or control group (CD). Lifestyle advisors reminded patients of medical visits to the primary care physician (PCP) and gave lifestyle advice by TSC or FFA. The CG received usual medical care. The outcome of this analysis was the drop-out rate from regular medical care. We estimated the HR and 95%
Stigmatization of Adults with Type 1 Diabetes in Asia

AMANDA Y. LAM, DAPHNE GARDNER, SURESH RAMA CHANDRAN, EDMUND P. TEO, LING ZHU, GERALD KOH, SU-YEN GOH, Singapore, Singapore

Background: Type 1 diabetes (T1D) is uncommon in Asia. Limited awareness can lead to stigmatization of those with T1D.

Aims: We aimed to evaluate diabetes stigma in adults with T1D in Singapore.

Methods: This was a cross-sectional sampling of adults with T1D in a tertiary public hospital, using the Type 1 Diabetes Stigma Assessment Scale (DSAS-1). Higher scores indicate greater levels of stigma.

Results: 125 Singaporeans (mean age 31.2 ± 11.2 y, 69% F), 107 on insulin injections, 18 on insulin pumps were sampled. Item response patterns (Figure) suggest a greater burden of stigma in the blame and judgment and identity concerns subscales. DSAS-1 scores did not differ by gender, treatment regimen, age, education level or employment. Identity concerns subscale scores were lower in those with T1D vs. those with Type 2 diabetes (T2D) (P < .01); BMI and BMI z-scores (P < .001) and systolic and diastolic blood pressure (SBP, DBP) (P < .05). DSAS-1 and subscale scores were similar to those of an Australian (D) cohort (n=960) (P<-.05). Total score 53.1 ± 12.9 vs. 53.0 ± 15.6, Treated differently 13.6 ± 4.0 vs. 13.6 ± 5.4, Blame and Judgment 19.9 ± 5.2 vs. 19.9 ± 6.0, and Identity Concerns: 19.8 ± 6.4 vs. 19.5 ± 7.2, all (P<.05).

Conclusion: This novel study documented significant levels of diabetes stigma among adults in Singapore, particularly relating to blame and judgment and identity concerns. Despite the low prevalence of T1D in Asia, levels of stigma appeared similar to that of an Australian T1D cohort.

QUEL14-263

Patient-Reported Outcomes in T2D Patients Inadequately Controlled by Metformin Are More Favorable for Dapagliflozin plus Saxagliptin vs. Insulin Glargine

MARICA A. TESTA, DONALD C. SIMONSON, ELLA EKHOLM, MAXWELL SU, EVA K. JOHNSSON, Boston, MA, Malmö, Sweden

Patients with T2D inadequately controlled by metformin require additional oral antidiabetic agents(s), injected GLP-1 or basal insulin. Although insulin has greater effect on A1C than a DPP-4 or SGLT2 inhibitor, its higher rates of hypoglycemia, weight gain and regimen burden might decrease satisfaction and quality of life. We analyzed patient-reported outcomes (PRO) from patients with T2D inadequately controlled by metformin ± sulfonylurea during an international, randomized, 24-week, open-label, non-inferiority trial (NCT02551874) of dapagliflozin plus saxagliptin add-on (DAPA + SAXA, n = 324) compared to titrated insulin glargine add-on (INS, n = 319). AIC and PRO questionnaires were obtained at baseline and weeks 12 and 24. Baseline data were: 54.0% male; 80.4% white; 60.7% working ≥3 days/week; age 55.5 ± 9.6 years; A1C 9.0 ± 1.0%; BMI 32.2 ± 5.3 kg/m2; diabetes duration 9.4 ± 6.3 years. Overall Satisfaction, Regimen Acceptance and its eight subscales, Net Benefit and Preference subscale, and Weight Concern all favored DAPA + SAGA at week 24 (Table). Quality of life scores favored DAPA + SAGA at week 12, but were not different at week 24. Compared to INS, DAPA + SAGA had greater treatment satisfaction and acceptance, better short-term quality of life, and less burden and concern about weight gain, hypoglycemia and pain despite comparable A1C.

Table. Change from Baseline in HbA1c and PRO at Week 24 [LS Mean (SE)]

<table>
<thead>
<tr>
<th>Category</th>
<th>Week 12</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C</td>
<td>-1.67 (0.08)</td>
<td>-1.54 (0.08)</td>
</tr>
<tr>
<td>Satisfaction</td>
<td>6.45 (0.69)</td>
<td>7.51 (0.63)</td>
</tr>
<tr>
<td>Side Effects</td>
<td>6.25 (0.52)</td>
<td>6.52 (0.52)</td>
</tr>
<tr>
<td>Weight</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Blame and Judgment</td>
<td>6.01 (0.63)</td>
<td>6.17 (0.63)</td>
</tr>
<tr>
<td>Identity Concerns</td>
<td>17.36 (0.61)</td>
<td>15.34 (0.68)</td>
</tr>
<tr>
<td>Total DSAS-1</td>
<td>8.01 (0.89)</td>
<td>2.95 (0.91)</td>
</tr>
<tr>
<td>Burden</td>
<td>7.70 (0.91)</td>
<td>2.48 (0.86)</td>
</tr>
<tr>
<td>– Regimen Acceptance</td>
<td>3.09 (0.73)</td>
<td>0.54</td>
</tr>
<tr>
<td>– Use</td>
<td>6.41 (0.94)</td>
<td>1.39 (0.96)</td>
</tr>
<tr>
<td>– Treatment</td>
<td>6.26 (0.86)</td>
<td>6.17 (0.83)</td>
</tr>
<tr>
<td>– Preference</td>
<td>13.08 (0.63)</td>
<td>15.34 (0.68)</td>
</tr>
<tr>
<td>– Side Effects</td>
<td>5.91 (0.71)</td>
<td>2.95 (0.91)</td>
</tr>
<tr>
<td>– Net Benefits</td>
<td>15.34 (0.68)</td>
<td>15.34 (0.68)</td>
</tr>
<tr>
<td>– Satisfaction</td>
<td>17.36 (0.61)</td>
<td>15.34 (0.68)</td>
</tr>
<tr>
<td>– Total</td>
<td>17.36 (0.61)</td>
<td>15.34 (0.68)</td>
</tr>
</tbody>
</table>
betes registry. Self-reported A1c, blog use, insulin pump use, CGM use, and sociodemographic factors were assessed. Univariate analysis evaluated for A1c differences between groups across variables including blog use, insulin pump use, and CGM use. Linear regression adjusted for significant covariates.

Results: 282 completed surveys were received (214 blog readers, 68 blog non-readers). A1c was lower for blog readers than blog non-readers (7.05 vs. 7.48, P=0.006), for insulin pump users than multiple daily injections (7.04 vs. 7.65, P=0.001), and for CGM users than CGM non-users (6.99 vs. 7.47, P=0.001). After adjusting for significant covariates, the association between blog use and A1c remained significant (P=0.039).

Conclusions: Reading T1D-themed blogs was found to be associated with glycemic control; self-reported A1c was 0.43% lower among blog readers than among blog non-readers, a clinically significant difference approaching the magnitude seen with CGM use (0.48%) and insulin pump use (0.61%). The A1c differences among pump users and CGM users in this study are similar to those found by others, lending support to the likelihood of a true association between A1c and blog use. To our knowledge, this is the first study to evaluate blog use and A1c and therefore the first to find an association between them. Further research should seek to explain the reasons for this association.

Supported By: National Institute of Diabetes and Digestive and Kidney Diseases; National Institutes of Health

Diabetes Distress and Glycemic Control in Working People with Type 1 Diabetes—The Role of Intentional Hyperglycemia at Work
ULLA M. HANSEN, KASPER OLESEN, TIMOTHY C. SKINNER, INGRID WILLAING, Gentofte, Denmark, Copenhagen, Denmark

Aims: We set out to test the hypothesis that intentional hyperglycemia at work (hereafter referred to as IHW) mediates the link between diabetes distress and glycemic control in working adults with type 1 diabetes.

Methods: Clinical information on HbA1c, complications, diabetes duration and age was linked with self-report measures of psychosocial health and work-life from people with type 1 diabetes of working age attending a specialist diabetes clinic in Denmark. Diabetes distress was assessed with a work-comprehensive measure encompassing the PAID-5 and two additional items assessing distress in reconciling diabetes and work life. IHW was assessed with one item. Glycemic control was assessed with HbA1c. Using structural equation modeling techniques we modelled a theory-based structural path model and tested the mediation hypothesis using bootstrap estimates and goodness-of-fit tests.

Results: The sample consisted of 1,126 working adults with type 1 diabetes. The model suggested that the effect of diabetes distress on glycemic control was fully mediated by IHW. Diabetes distress was associated with more frequent IHW (β=.23, P<.001) which in turn was associated with elevated HbA1c (β=.28, P<.001). The final model was able to account for 20% of the variance of IHW, and 11% of the variance in glycemic control. There was an excellent fit to the data according to established criteria (χ²=83.2, df=74, p=0.3, CFI=.99, RMSEA=.047 (0.030–0.065), 95% CI).

Discussion: This study highlights the role of IHW as a mediator for the link between diabetes distress and glycemic control specific to working adults with type 1 diabetes. A sound understanding of the mechanisms linking diabetes distress to suboptimal glycemic control in working people with type 1 diabetes can inform intervention development and ultimately increase the chance of improving diabetes self-care and quality of life of working people with type 1 diabetes.

Supported By: Innovation Fund Denmark

Sleep and Glycemia in Adolescents with Type 1 Diabetes
MARGARET GREY, KAITLYN RECHENBERG, West Haven, CT

Nearly 70% of adolescents have chronic sleep problems (quality, quantity, and/or altered circadian rhythm). Adolescents with type 1 diabetes (T1D) are subject to nocturnal blood glucose fluctuations that may result in restless sleep and require self-care that disrupts sleep. Deficient sleep may also be deficient sleep/wake cycles using 30-second epochs, and a continuous glucose monitor (CGM). The Pittsburgh Sleep Quality Index (PSQI) was used to assess subjective sleep reports. The sample included 30 participants age ≥13 years of age with type 1 diabetes. A212

Anxiety in Adolescents with Type 1 Diabetes
KAITLYN RECHENBERG, LOIS S. SADLER, MARGARET GREY, West Haven, CT, Orange, CT

Adolescents with type 1 diabetes (T1D) are at a high risk of psychosocial comorbidity, e.g., anxiety, depression, and eating disorders. Anxiety symptoms have been associated with poorer glycemic control. Anxiety symptoms have not been well studied in these youth. Our aim was to describe the experience of anxiety symptoms in adolescents with T1D, especially related to diabetes self-management and sleep patterns.

We used qualitative description, consisting of 10 open-ended questions, the State-Trait Anxiety Inventory for Children (STAIc), and Hemoglobin A1c (A1c). The analysis was guided by the principles of thematic analysis. Demographic data, A1c, and STAIc scores were used to stratify the qualitative data. Adolescents with T1D (ages 10-16) were recruited from the Yale Program. Twenty-nine participants were interviewed. Participants were mean age 13.6±3.9 years, 32% minority, 31% lower socioeconomic status (SES), A1c 8.3±3.3%, mean disease duration 5.6±3.7 years, mean state anxiety 47.1±4.5, and mean trait anxiety 32.8±8.2.

Four themes and 7 sub-themes emerged. Participants reported that T1D was an extra layer of responsibility that took time away from their ability to participate fully in other aspects of their lives. Some participants were able to integrate diabetes management into their lives, while others were not. Participants noted that their experience of anxiety was associated with poor quality sleep, general lifestyle factors, diabetes, or all of these. Exploratory stratified analyses based on levels of STAIc findings revealed that: adolescents with high state anxiety were from lower SES single-parent families and all reported poor sleep and high A1c levels (≥8.9%), those with low state anxiety were from higher SES families with two parents, all had low A1c levels (<7.5%), and all were still managed by their parents.

Associations between anxiety symptoms and poorer self-management should be confirmed with further data. Increased screening and interventions for anxiety symptoms might be warranted.

Distress, Depression, or Both? Exploring Differences in the DDS-17 and the PHQ-9 in Diabetes Specialty Clinic
JANA L. WARDIAN, KATHRYN E. KANZLER, TOM J. SAUERWEIN, MARK W. TRUE, MICHAEL A. GLOTTEREL, San Antonio, TX, Dayton, OH

Diabetes-related distress (DRD) is distinctly different from depression and is more common than depression in people with diabetes. DRD has serious negative outcomes, including poor glycemic control. DRD has been identified in more than 40% of people with diabetes. Recent ADA Standards recommend assessing and addressing DRD; however, in clinical settings, confusion may exist concerning utility of screening for DRD. This study explores differences in our population between scores on DRD and depression screening measures. At the USAF Diabetes Center of Excellence (DCOE), a military specialty clinic, adult patients were administered the Patient Health Questionnaire (PHQ-9) and the Diabetes-related Distress Scale (DDS-17) as part of standard care from June 2015 through August 2016. Distinct areas of DRD are: 1.) Emotional Burden (EB); 2.) Physician-related Distress (PD); 3.) Regimen-related Distress (RD); and 4.) Interpersonal Distress (ID). DDS-17 was categorized as <2.0=little

Supported By: National Institutes of Health

A212
or no distress; 2.0-2.9=moderate distress; and ≥3=high distress. A score ≥ 10 was considered positive for depression on the PHQ-9. Participants with high distress were more likely to have diabetes and to be obese. This suggests that psychological distress may increase the risk of type 2 diabetes.

Methods: Adults with T2D who enrolled in a randomized controlled trial of a 10-year ILI intervention compared with diabetes support and education (DSE; N=5,084; AL, Baton Rouge, LA, Memphis, TN, Minneapolis, MN). The ILI program aimed to increase physical activity, improve dietary habits, and provide education on self-management. The DSE program provided basic diabetes education and monitoring. The study also included a control group.

Results: At baseline, 12%, 16%, and 23% of all participants reported some distress; 2.0-2.9=moderate distress; and ≥3=high distress. A score ≥ 10 was considered positive for depression on the PHQ-9. Participants with high distress were more likely to have diabetes and to be obese. This suggests that psychological distress may increase the risk of type 2 diabetes.

Methods: Adults with T2D who enrolled in a randomized controlled trial of a 10-year ILI intervention compared with diabetes support and education (DSE; N=5,084; AL, Baton Rouge, LA, Memphis, TN, Minneapolis, MN). The ILI program aimed to increase physical activity, improve dietary habits, and provide education on self-management. The DSE program provided basic diabetes education and monitoring. The study also included a control group.

Results: At baseline, 12%, 16%, and 23% of all participants reported some distress; 2.0-2.9=moderate distress; and ≥3=high distress. A score ≥ 10 was considered positive for depression on the PHQ-9. Participants with high distress were more likely to have diabetes and to be obese. This suggests that psychological distress may increase the risk of type 2 diabetes.
Conclusion: DPN was higher in the poor sleep quality group. Other diabetic complications showed no significant difference in both groups.

Table.

<table>
<thead>
<tr>
<th>Table</th>
<th>PSQI ≤ 5 (n = 68)</th>
<th>PSQI &gt; 5 (n = 83)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>54.7 ± 16.6</td>
<td>53.3 ± 14.8</td>
<td>0.684</td>
</tr>
<tr>
<td>Male/Female, n</td>
<td>31/37</td>
<td>54/49</td>
<td>0.544</td>
</tr>
<tr>
<td>Duration of Diabetes, years</td>
<td>8.3 ± 5.4</td>
<td>7.4 ± 4.8</td>
<td>0.557</td>
</tr>
<tr>
<td>Inulin use, %</td>
<td>34.3</td>
<td>39.5</td>
<td>0.516</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>52.9</td>
<td>47.0</td>
<td>0.467</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.6 ± 3.7</td>
<td>25.8 ± 4.2</td>
<td>0.003</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>0.82 ± 0.07</td>
<td>0.82 ± 0.09</td>
<td>0.133</td>
</tr>
<tr>
<td>Glycated hemoglobin, %</td>
<td>101.2 ± 2.2</td>
<td>103.3 ± 2.6</td>
<td>0.623</td>
</tr>
<tr>
<td>Glycated albumin, %</td>
<td>30.6 ± 11.4</td>
<td>30.8 ± 14.2</td>
<td>0.904</td>
</tr>
<tr>
<td>Fasting plasma glucose, mg/dL</td>
<td>186.1 ± 74.5</td>
<td>181.6 ± 66.5</td>
<td>0.704</td>
</tr>
<tr>
<td>Fasting insulin, µU/mL</td>
<td>9.29 ± 5.33</td>
<td>12.00 ± 8.34</td>
<td>0.007</td>
</tr>
<tr>
<td>Fasting c-peptide, ng/mL</td>
<td>1.8 ± 1.4</td>
<td>2.5 ± 2.4</td>
<td>0.045</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>171.8 ± 45.7</td>
<td>201.8 ± 110.1</td>
<td>0.253</td>
</tr>
<tr>
<td>LDL-cholesterol, mg/dL</td>
<td>97.8 ± 34.8</td>
<td>94.2 ± 34.1</td>
<td>0.524</td>
</tr>
<tr>
<td>HDL-cholesterol, mg/dL</td>
<td>41.7 ± 12.3</td>
<td>41.2 ± 11.1</td>
<td>0.794</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>154.3 ± 83.3</td>
<td>264.9 ± 175.8</td>
<td>0.013</td>
</tr>
<tr>
<td>Mean carotid intima-media thickness, mm</td>
<td>0.54 ± 0.13</td>
<td>0.54 ± 0.12</td>
<td>0.783</td>
</tr>
<tr>
<td>Brachial-ankle pulse wave velocity, cm/s</td>
<td>1362.7 ± 372.0</td>
<td>1394.7 ± 398.7</td>
<td>0.701</td>
</tr>
<tr>
<td>Presence of microalbuminuria, mg/L</td>
<td>37.7</td>
<td>27.9</td>
<td>0.253</td>
</tr>
<tr>
<td>Presence of diabetic retinopathy, %</td>
<td>46.8</td>
<td>43.9</td>
<td>0.763</td>
</tr>
<tr>
<td>Presence of diabetic neuropathy, %</td>
<td>15.2</td>
<td>31.7</td>
<td>0.020</td>
</tr>
<tr>
<td>Presence of fatty liver disease, %</td>
<td>72.5</td>
<td>64.3</td>
<td>0.337</td>
</tr>
</tbody>
</table>

**821-P**

**Relationship between Weight Change Patterns and Health Satisfaction in the CANadian Canagliflozin Registry (CanCARE) Study**

VINCENT C WOO, HARPREET S BAJAJ, MAUREEN A CLEMENT, FERNANDO CAMACHO, SHANA TRAINA, NATASHA GEORGIJEV, JENNIFER B ROSE, DELNA SORABJI, ALAN D BELL, WINNY MB, CANADA Brampton, ON, CANADA, Coldstream, BC, Canada, Waterloo ON, Canada, Rantau, NJ, Toronto ON, Canada

Patient health satisfaction is associated with positive health behaviors and is considered important for optimal management of type 2 diabetes mellitus (T2DM). In previously reported randomized clinical trials (RCTs) of canagliflozin (CANA), CANA reduced HbA1C, body weight, and blood pressure. CanCARE is a prospective, observational, 12-month registry for people living with T2DM newly initiated on CANA. The Current Health Satisfaction Questionnaire (CHES-Q) was administered in this study at baseline (BL) and repeated at 3, 6 and 12 months. We report the pre-specified analyses investigating the relationship between current health satisfaction agreement on CHES-Q with weight change patterns defined as: Pattern 1 (loss from BL to month 3 and loss from month 3 to 12); Pattern 2 (loss from BL to month 3 and gain from month 3 to 12); Pattern 3 (gain from BL to month 3 and loss from month 3 to 12); and Pattern 4 (gain from BL to month 12).

At month 12, 75.4% of subjects (389/516) completed the CHES-Q, of which 3/4 of subjects with available data, had a mean weight loss of 3.2 kg (7.1 lbs). Proportion of subjects with weight loss patterns were 55.5%, 25.5%, 13.2% and 4.8% for patterns 1, 2, 3, and 4, respectively. Satisfaction agreement with current health increased from 46.5% to 67.9%, 52.5% to 63.9%, 40.0% to 4% for patterns 1, 2, 3, and 4, respectively. Satisfaction agreement with health improved with greater weight loss and was consistent with that seen in CANA RCTs and suggests a direct correlation between weight change patterns and health satisfaction for people living with T2DM.

**822-P**

**Cognitive Function Is Impaired in Recently Diagnosed Type 2 Diabetes, but Not in Type 1 Diabetes**

THERESA VAN DEMERT, WOLFGANG WÖLWER, KATHARINA S. WEBER, ANNIKKA HÖYER, KLAUS STRASSBURGER, NORA T. BOHNHAU, MARIE BRÜGGEN, KATHARINA OVELGOENNE, EVA-MARIA GÖSSMANN, VOLKER BURKART, JULIA SzenZDORÖDI, MICHAEL RODEN, KARSTEN MÜSSLIG, Düsseldorf, Germany

Diabetes associates with higher risk of dementia. We hypothesized that cognitive function is already impaired during the early course of diabetes. Thus, we performed a cross-sectional analysis within the German Diabetes Study including patients within the first year after diagnosis of type 1 (n=82) or type 2 (n=119) diabetes, patients with type 1 (n=45) or type 2 (n=65) diabetes five years after study inclusion and metabolically healthy humans (n=42). Participants underwent comprehensive metabolic phenotyping and testing of different domains of cognitive function. Cognition test outcomes were compared using linear regression models with age, sex, and crystallized intelligence as independent variables. Furthermore, within the groups, associations between cognitive function and age, sex, body mass index (BMI), insulin sensitivity, high-sensitivity C-reactive protein, hemoglobin A1c, and crystallized intelligence were studied using linear regression analysis. In participants with recently diagnosed diabetes, verbal memory was poorer in patients with type 2 diabetes (P=0.029), but not in type 1 diabetes (P=0.146) when compared to healthy individuals. Five years after diagnosis, type 2 diabetes patients also showed decreased verbal memory than those with type 1 diabetes (P=0.013). In addition to crystallized intelligence, a higher BMI among those recently diagnosed type 2 diabetes were associated with impaired verbal memory (all P<0.05).

In conclusion, verbal memory is impaired in individuals with recently diagnosed type 2 diabetes and likely associated with higher body mass. Supported By: German Ministry of Culture and Science of the State of North Rhine-Westphalia; German Federal Ministry of Health; German Federal Ministry of Education and Research

**823-P**

**Education for Family Members Is Effective for Improved Glycemic Control of Patients with Type 2 Rather Than Type 1 Diabetes Mellitus—A Meta-analysis**

SATORU KODAMA, SR, KAZUYA FUJIHARA, HAJIME ISHIKAWA, CHIKAOHORIKAWA, YOKO YACHI, MASAIRO SHIZAWA, SATOSHI MATSUNAGA, SHIRO TANAKA, KIM-INDORI KATO, HIRUTAKONE SUNE, Akiyama, Japan, Chiba, Japan, Kyoto, Japan

Although the importance of support of patients by family members is emphasized for diabetes care, evidence of achieving adequate glycemic control through instruction family members to help in self-management care of diabetes patients has not been established. This meta-analysis assessed the effect of family-oriented diabetes programs on GC. The pooled A1C change shown in 31 studies that were retrieved from systematic literature searches for clinical trials presenting data on the net effect of family education on the reduction in glycormoglobin A1c (A1C), i.e., difference in A1C change between intervention groups involving family members and that not involving family members [control group] was -0.45% (P<0.001). When separating trials limited to type 1 and type 2 diabetes, the pooled A1C values were -0.35% (P<0.001) and -0.71% (P=0.001), respectively (Figure). Current meta-analysis indicates that involving family members in diabetes education programs is an effective strategy for improved GC predominantly in patients with type 2 diabetes. Figure legend: Forest plot of differences in changes in A1C between intervention and control groups. Effect size below zero indicates an A1C reduction larger in the intervention group than in the control group.
Impact of rtCGM Usage on a Combined Patient Reported Outcome—
A Post-Hoc Analysis of the HypoDE Study
DOMINIC EHRMANN, LUTZ HEINEMANN, GUIDO FRECKMANN, DELIA WALDEN-MAIER, NORBERT HERMANNS, Bad Mergentheim, Germany; Düsseldorf, Düsseldorf, Germany

The HypoDE study, a randomized multi-center trial, showed that rtCGM use reduces the number of low glucose events (<55 mg/dl for at least 20 min) per 28 days significantly from 10.4 to 3.4 events compared to SMBG (13.5 to 13.2 events) in MDI-treated type 1 diabetic patients with hypoglycemia problems. We analyzed the impact of rtCGM use on patient-reported-outcomes (PRO). A combined PRO consisting of a specific measure of satisfaction with glucose monitoring (GMSS), a diabetes-specific assessment (DDS) and a generic measure (EG-SD) was used. In a factor analysis, all three scales loaded on one factor. All questionnaire scores were z-transformed as well as the number of low glucose events. The Figure shows the effect sizes of the combined PRO and the single scores as well as of the low glucose events. There was a significant positive impact of rtCGM use on the combined PRO. However, only GMSS but not DDS or EG-SD showed a significant impact. The more device-specific the PRO, the higher was the effect size. Interestingly, the impact of rtCGM use on biochemical hypoglycemia had a remarkably larger effect size than the combined PRO. Since most other rtCGM studies are powered to detect a benefit in glycemic endpoints and not in PRO, the lower impact of rtCGM on PRO is a barrier to prove the efficacy of rtCGM on PRO like quality of life, diabetes distress or satisfaction with treatment.

Figure.

Supported By: Dexcom, Inc.

Comprehensive Diabetes Stigma Scale—Associations with Patient Characteristics and Outcomes
LAUREN B. BEACH, SHYAM KANKOTIA, CHRISTINE U. DINH, TOM ELASY, LINDSAY S. MAYBERRY, KENNETH WALLSTON, GREGORY PHILLIPS II, PATRICK JANULIS, KERRI CAVANAUGH, Chicago, IL, Providence, RI; Iowa City, IA, Nashville, TN, Pisgah Forest, NC

Stigma related to health conditions has been linked to poor medication adherence and health outcomes. With input from patients living with diabetes, diabetes clinicians, and stigma researchers, we designed the Comprehensive Diabetes Stigma Scale (CDSS). We hypothesized that higher diabetes stigma would be associated with worse medication adherence, younger age, insulin use, and higher HbA1c values. We recruited adults with diabetes on insulin medication in person from one academic practice and online via ResearchMatch. Participants completed the 15-item CDSS and measures of perceived diabetes stigma from family members, psychological and behavioral consequences of diabetes stigma, and medication adherence. Participants self-reported the range of their most recent HbA1c lab value. Spearman correlations and multiple linear regression were used to assess associations between variables. Participants (n=311) were on average 61±11 years; 56% female and 86% white. Most (69%) participants endorsed at least 1 CDSS-15 item, 34% reported HbA1c >7.0%, and 49% reported insulin use. CDSS-15 scores correlated with diabetes family perceived stigma (ρ=0.51, p<0.01) and consequences of diabetes stigma (ρ=0.63, p<0.01). Higher diabetes stigma correlated with worse medication adherence (ρ=0.40, p<0.01). This association remained significant after adjusting for age, sex, race, diabetes duration, insulin use, and marital, employment, and insurance status (β=0.17, p<0.01). By age, younger participants had higher CDSS-15 scores (ρ=0.35, p<0.01). CDSS-15 scores did not differ by insulin use status (ρ=0.03, p=0.98). The mean CDSS-15 score of participants with HbA1c <6.4% (23; 95% CI 21-25) was lower than those with HbA1c >9.0% (30; 95% CI 19-41), but this difference was not significant (p=0.06). These findings reinforce that diabetes stigma is prevalent and show for the first time that diabetes stigma may be a unique factor contributing to suboptimal diabetes medication adherence.

Supported By: National Institutes of Health; National Institute of Diabetes and Digestive and Kidney Diseases (DK029286, T35DK007383, DK02583, T32DK007569, DK063036); National Center for Advancing Translational Sciences (UL1TR000445)

Acceptability of a Self-Regulation Theory-Based mHealth Behavior Intervention for Older Adults with Type 2 Diabetes and Obesity
YANGUI ZHENG, KATIE WEINGER, MATT C. GREGAS, JORDAN GREENBERG, ZHUOXIN LI, LORA E. BURKE, CHENFANG QI, CHRISTINE SLYNE, TORI GREEVES, MEDHA MUNISHI, Chestnut Hill, MA; Boston, MA; Brighton; MA; Pittsburg, PA

Behavioral Medicine: Clinical, Nutrition, Education, and Exercise

The HypoDE study, a randomized multi-center trial, showed that rtCGM reduce the number of low glucose events (<55 mg/dl for at least 20 min) per 28 days significantly from 10.4 to 3.4 events compared to SMBG (13.5 to 13.2 events) in MDI-treated type 1 diabetic patients with hypoglycemia. We analyzed the impact of rtCGM use on patient-reported-outcomes (PRO). A combined PRO consisting of a specific measure of satisfaction with glucose monitoring (GMSS), a diabetes-specific assessment (DDS) and a generic measure (EG-SD) was used. In a factor analysis, all three scales loaded on one factor. All questionnaire scores were z-transformed as well as the number of low glucose events. The Figure shows the effect sizes of the combined PRO and the single scores as well as of the low glucose events. There was a significant positive impact of rtCGM use on the combined PRO. However, only GMSS but not DDS or EG-SD showed a significant impact. The more device-specific the PRO, the higher was the effect size. Interestingly, the impact of rtCGM use on biochemical hypoglycemia had a remarkably larger effect size than the combined PRO. Since most other rtCGM studies are powered to detect a benefit in glycemic endpoints and not in PRO, the lower impact of rtCGM on PRO is a barrier to prove the efficacy of rtCGM on PRO like quality of life, diabetes distress or satisfaction with treatment.

Figure.

Supported By: Boston College

Comprehensive Diabetes Stigma Scale—Associations with Patient Characteristics and Outcomes
LAUREN B. BEACH, SHYAM KANKOTIA, CHRISTINE U. DINH, TOM ELASY, LINDSAY S. MAYBERRY, KENNETH WALLSTON, GREGORY PHILLIPS II, PATRICK JANULIS, KERRI CAVANAUGH, Chicago, IL, Providence, RI; Iowa City, IA, Nashville, TN, Pisgah Forest, NC

Stigma related to health conditions has been linked to poor medication adherence and health outcomes. With input from patients living with diabetes, diabetes clinicians, and stigma researchers, we designed the Comprehensive Diabetes Stigma Scale (CDSS). We hypothesized that higher diabetes stigma would be associated with worse medication adherence, younger age, insulin use, and higher HbA1c values. We recruited adults with diabetes on insulin medication in person from one academic practice and online via ResearchMatch. Participants completed the 15-item CDSS and measures of perceived diabetes stigma from family members, psychological and behavioral consequences of diabetes stigma, and medication adherence. Participants self-reported the range of their most recent HbA1c lab value. Spearman correlations and multiple linear regression were used to assess associations between variables. Participants (n=311) were on average 61±11 years; 56% female and 86% white. Most (69%) participants endorsed at least 1 CDSS-15 item, 34% reported HbA1c >7.0%, and 49% reported insulin use. CDSS-15 scores correlated with diabetes family perceived stigma (ρ=0.51, p<0.01) and consequences of diabetes stigma (ρ=0.63, p<0.01). Higher diabetes stigma correlated with worse medication adherence (ρ=0.40, p<0.01). This association remained significant after adjusting for age, sex, race, diabetes duration, insulin use, and marital, employment, and insurance status (β=0.17, p<0.01). By age, younger participants had higher CDSS-15 scores (ρ=0.35, p<0.01). CDSS-15 scores did not differ by insulin use status (ρ=0.03, p=0.98). The mean CDSS-15 score of participants with HbA1c <6.4% (23; 95% CI 21-25) was lower than those with HbA1c >9.0% (30; 95% CI 19-41), but this difference was not significant (p=0.06). These findings reinforce that diabetes stigma is prevalent and show for the first time that diabetes stigma may be a unique factor contributing to suboptimal diabetes medication adherence.

Supported By: National Institutes of Health; National Institute of Diabetes and Digestive and Kidney Diseases (DK029286, T35DK007383, DK02583, T32DK007569, DK063036); National Center for Advancing Translational Sciences (UL1TR000445)

Acceptability of a Self-Regulation Theory-Based mHealth Behavior Intervention for Older Adults with Type 2 Diabetes and Obesity
YANGUI ZHENG, KATIE WEINGER, MATT C. GREGAS, JORDAN GREENBERG, ZHUOXIN LI, LORA E. BURKE, CHENFANG QI, CHRISTINE SLYNE, TORI GREEVES, MEDHA MUNISHI, Chestnut Hill, MA; Boston, MA; Brighton; MA; Pittsburg, PA

Behavioral Medicine: Clinical, Nutrition, Education, and Exercise

The HypoDE study, a randomized multi-center trial, showed that rtCGM reduce the number of low glucose events (<55 mg/dl for at least 20 min) per 28 days significantly from 10.4 to 3.4 events compared to SMBG (13.5 to 13.2 events) in MDI-treated type 1 diabetic patients with hypoglycemia. We analyzed the impact of rtCGM use on patient-reported-outcomes (PRO). A combined PRO consisting of a specific measure of satisfaction with glucose monitoring (GMSS), a diabetes-specific assessment (DDS) and a generic measure (EG-SD) was used. In a factor analysis, all three scales loaded on one factor. All questionnaire scores were z-transformed as well as the number of low glucose events. The Figure shows the effect sizes of the combined PRO and the single scores as well as of the low glucose events. There was a significant positive impact of rtCGM use on the combined PRO. However, only GMSS but not DDS or EG-SD showed a significant impact. The more device-specific the PRO, the higher was the effect size. Interestingly, the impact of rtCGM use on biochemical hypoglycemia had a remarkably larger effect size than the combined PRO. Since most other rtCGM studies are powered to detect a benefit in glycemic endpoints and not in PRO, the lower impact of rtCGM on PRO is a barrier to prove the efficacy of rtCGM on PRO like quality of life, diabetes distress or satisfaction with treatment.

Figure.

Supported By: Dexcom, Inc.
Prevalence and Factors Associated with Sleep Disorders in Japanese Patients with Type 2 Diabetes

HIDEYUKI ITAKA, HIROYUKI MIYAKAMI, SATORU MIZUSHIRI, AYA KAMBA, MAKOTO DAIMON, Hinatsuki, Japan, Nachinoko, Japan

Background: Sleep disorders are frequently reported in patients with type 2 diabetes. However, there are few reports on the prevalence and correlates of sleep disorders in diabetics. This study investigated the prevalence and factors associated with sleep disorders in type 2 diabetes.

Research Design and Methods: In total, 544 patients with type 2 diabetes mellitus (311 males, 233 females; age 63.9 ± 12.6-years-old; HbA1c, 7.1 ± 0.9%) and 1,161 control subjects (38.1% males; 54.5 ± 14.8-years-old; HbA1c 5.6 ± 0.6%) were included. Participants used self-administered questionnaires on sleep attitude (Pittsburgh Sleep Quality Index, PSQI), quality of life (the Short Form 36 Health Survey; SF-36), depression (the Center for Epidemiologic Studies-Depression scale), and personality (Ten Item Personality Inventory). The socio-demographics, laboratory data, and medical history were collected from medical records.

Results: The number of subjects with sleep disorders (PSQI > 5) was higher in diabetic patients (25.9%) than control subjects (20.6%) (p = 0.02), although sleeping time was significantly longer in diabetic (7.42 hours) than in control subjects (7.09 hours) (p < 0.01). Among diabetic patients, the sleep disorders group showed higher percentages of females (p < 0.01), spouses (p = 0.01), insulin users (p < 0.01), depression (p < 0.01), overactive bladder (p < 0.01), and benign prostatic hyperplasia (p < 0.01). Diabetic patients with sleep disorders scored higher on the neuroticism scale compared to patients without sleep disorders (p < 0.01). All SF-36 scores were lower in patients with sleep disorders compared to controls. No differences were found in age, body mass index, HbA1c, stage of diabetic retinopathy, and nephropathy between patients with the presence or absence of sleep disorders.

Conclusions: The prevalence of sleep disorders was high in patients with type 2 diabetes, and their quality of life was impaired. Therefore, clinicians should monitor sleep disorders among these patients.

Impact of Diabetes-Related Distress on Predicted Cardiovascular Complications in Patients with Type 2 Diabetes

CLIFFER YOUNG, JOY A. DUSAN, ANDREW J. RAY, JAY H. SHUBRICK, Vallejo, CA

Objective: To evaluate the impact of diabetes-related distress along with other cardiovascular risk factors on the predicted 10-year cardiovascular complication risks in patients with type 2 diabetes.

Methods: This cross-sectional study involved Problem Areas in Diabetes (PAID) questionnaire and UK Prospective Diabetes Study (UKPDS) Risk Engine 2.0, surveying a population with lower socioeconomic status and type 2 diabetes. Statistical analyses incorporated multiple linear regression models, comprising of the predicted cardiovascular risks, PAID scores, tobacco use, gender, age, LDL levels, clinically documented depression status, BMI, and systolic blood pressure.

Results: Results are organized by statistical models (driven by risk factors for cardiovascular conditions) and the predicted, individual 10-year cardiovascular complication risks vs. PAID scores. Conclusion: This study found an association between psychosocial status and cardiovascular disease risk management in lower socioeconomic patients with type 2 diabetes. Within all the multiple linear regression models, the levels of diabetes-related distress have been shown to impact the predicted fatal coronary heart disease risks, thus allowing this distress to predict such cardiovascular risk after including certain risk factors.

Table.

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>p-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression Status, Tobacco Use, LDL Levels, Gender, Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predicted Coronary Heart Disease Risks vs. PAID Scores</td>
<td>0.077</td>
<td>0.039</td>
</tr>
<tr>
<td>Predicted Fatal Coronary Heart Disease Risks vs. PAID Scores</td>
<td>0.070</td>
<td>0.014</td>
</tr>
<tr>
<td>Predicted Stroke Risks vs. PAID Scores</td>
<td>0.016</td>
<td>0.38</td>
</tr>
<tr>
<td>Predicted Fatal Stroke Risks vs. PAID Scores</td>
<td>0.007</td>
<td>0.62</td>
</tr>
<tr>
<td>Systolic Blood Pressure, Tobacco Use, LDL Levels, Gender, Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predicted Coronary Heart Disease Risks vs. PAID Scores</td>
<td>0.068</td>
<td>0.069</td>
</tr>
<tr>
<td>Predicted Fatal Coronary Heart Disease Risks vs. PAID Scores</td>
<td>0.063</td>
<td>0.029</td>
</tr>
<tr>
<td>Predicted Stroke Risks vs. PAID Scores</td>
<td>0.015</td>
<td>0.388</td>
</tr>
<tr>
<td>Predicted Fatal Stroke Risks vs. PAID Scores</td>
<td>0.0019</td>
<td>0.495</td>
</tr>
</tbody>
</table>

Health Mindset and Health Outcomes for Adolescents with Type 1 Diabetes

LAURA NALLY, CLAUDIA MUELLER, Stanford, CA

Background: Health mindset theory is a novel approach to the study of health outcomes in pediatric populations. Health mindsets have been found to influence how individuals perceive illness and have been linked to health outcomes in adolescents with T1D. Specifically, individuals with a “fixed” mindset of health view illness more negatively and have worse outcomes than those with a “growth” mindset who believe that health can be improved through effort.

Methods: A cohort of adolescents with T1D was followed across the transition from pediatric to adult care to assess differences in their health outcomes over time. We predicted that having a growth mindset would be a protective factor for young adults as they take greater control over their health care.

Results: Ninety-one participants aged 12-19 with T1D were recruited, with 70 transitioning to adult care during the study period. 61% had a growth mindset while 39% had a fixed mindset of health. Overall, average A1c after transition was lower for participants with a growth vs. a fixed mindset. The most notable difference was found for participants who had the highest A1c before transition (>10%). In this group, growth-mindset adolescents showed a significant improvement in A1c levels compared to those with a fixed mindset (p<.05). Further, a greater percentage of adolescents with a growth (28%) vs. a fixed (9%) mindset was able to reach a target A1c of less than 7%. Age at time of transition (Mean=19 years) was similar for those with fixed and growth mindsets.

Conclusion: In this study of adolescents with T1D, having a growth mindset was linked to better glycemic outcomes after transitioning to adult care. Improvement in A1c was greatest for those young adults with a growth mindset who had the poorest glycemic control before transition. This suggests that health mindset might interact with changes in age or maturity level, particularly for young adults, and so may prove to be a powerful target for efforts to improve health maintenance in this population.
Gender Differences in Psychosocial Factors Influencing Glycemic Control among Chinese Adults with Type 2 Diabetes Mellitus
KEKE LIN, LAURIE T. QUINN, Beijing, China, Chicago, IL
Identifying gender differences in psychosocial factors associated with glycemic control will help to develop gender-specific interventions to achieve optimal glycemic control for people with type 2 diabetes (T2DM). This study aimed to examine the differences between males and females in terms of diabetes self-efficacy, perceived role demands, attitudinal familialism, diabetes distress, and family support among a group of Chinese adults with T2DM. A convenience sample of 210 patients with T2DM (male=99, female=111) was recruited from a community health center in Beijing, China. Study instruments included Self-efficacy Scale for Patients with T2DM, Perceived Role Demands Scale, Attitudinal Familism Scale, Diabetes Distress Scale, and Diabetes Family Behavior Checklist-II. The statistical methods included descriptive analysis, t-test and Wilcoxon rank-sum test. Females had higher attitudinal familialism scores (t=-2.12, p<0.05), higher number of roles (Z=-2.33, p<0.01), and more perceived role demands related to caregiving (Z=-4.44, p<0.001) than males. Conversely, males had a significantly higher family supportive behaviors mean score (Z=2.76, p<0.1) and more perceived role demands related to jobs (Z=4.18, p<0.001) than females. There were no statistically significant gender differences in terms of diabetes distress (t=-1.04, p>0.05) and self-efficacy (t=-0.08, p>0.05). These findings indicated that females struggled more with caregiving responsibilities, were more likely to put family interest above their own health needs, yet received less family support than males. Clinicians should take these gender differences into account when designing interventions that address diabetes self-management and glycemic control.

832-P Positive Impact of Integrative Medicine Approaches on Diabetes Related Care
JEONG-HEE KU, MATTHEW FREEBY, RASHMI S. MULLUR, Los Angeles, CA
Patients with diabetes have higher prevalence of depression and diabetes-related distress that negatively impacts care. Mindfulness-based approaches have shown to improve depression, diabetes-related distress, and in small studies also improve glycemic outcomes. We created a 90-minute, shared medical appointment, led by an endocrinologist, teaching patients integrative approaches to manage diabetes-related distress. We included patients with type 2 diabetes referred by a primary care provider or an endocrinologist, and assessed Diabetes Distress Scale (DDS), Patient Health Questionnaire-9 (PHQ-9) as well as Hemoglobin A1C (HbA1C), weight, blood pressure (BPI), heart rate (HR) before the group visit.

Thirty-four patients attended group sessions, with mean age of 63.9 years, mean baseline HbA1c 7.7% and mean BMI 33.3. The mean DDS was 36.2, and mean PHQ-9 was 7.8. Twenty-four patients followed up in clinic 3 months after initial appointment and showed mean reduction in HbA1c by 0.18% (p=0.35). Subgroup analysis of patients with baseline HbA1c ≥7.5% (n=11) showed mean reduction in HbA1c by 0.8% (p=0.005). No statistically significant changes in BP, HR or weight were seen, while a subgroup (n=11) showed mean reduction in HbA1c by 0.8% (p=0.005). No statistically significant changes in BP, HR or weight were seen, while a subgroup (n=11) showed mean reduction in HbA1c by 0.8% (p=0.005). No statistically significant changes in BP, HR or weight were seen, while a subgroup (n=11) showed mean reduction in HbA1c by 0.8% (p=0.005).

Conclusion: Increasing step counts by more than 3000 steps/day resulted in improvement in HbA1c and aortic BP and stiff ness in middle-aged Chinese men with type 2 diabetes mellitus (T2DM).

Exploring Psychological Aspects of Hyperglycemia in People with Type 2 Diabetes
METTE A. NEXO, BRYAN CLEAY, INGRID WILLAING, Gentofte, Denmark
Objective: The psychological dimension of hyperglycemia is poorly investigated. This study explored how individuals with type 2 diabetes (T2D) experienced and respond psychologically to hyperglycemia.
Method: From a larger study investigating T2D and work life we purposefully selected 7 individual interviews eligible for Interpretative Phenomenological Analysis (IPA). Interviews providing rich and detailed data regarding the subjective experience of hyperglycemia were included. Participants were recruited from a Danish diabetes clinic and had at least 2 years duration of T2D and minimum 1 documented complication. Two researchers independently analyzed each individual case. Contradictions and variations of the analyses were then compared at three levels of analysis: Experiential, linguistic and interpretative. Superordinate themes were developed, if the essence of themes were generaliziable across accounts.

Results: Three superordinate themes emerged: Theme 1 'High blood sugar sh Ascribed Negative Personality Characteristics or
emotional reactions were ascribed negative personality characteristics or poor self-care abilities and threatened the concept of self. Theme 3 'Emotional Distress'. The cognitive reactions triggered a wide range of distressing emotions; mainly shame, guilt and sadness.

Conclusion: These results are the first to document the cognitive and emotional responses to hyperglycemia and can potentially inform psychological interventions targeting people with T2D. However, IPA is an idiographic approach generating theory from few homogenous cases and further studies are needed to generalize beyond the individual level.
RESULTS: Patients with an A1c of <8% (n=193) were less likely than those with an A1c of 7.9-9.9% (n=184) or an A1c of <7% (n=231) to agree that they know how to control their T2DM (p<0.05). They were also less likely to report maintaining a healthy diet, being able to achieve their desired weight, and taking their T2DM medications as recommended. Patients with an A1c ≥8% were also less likely to agree they have a good relationship with their HCP, that they keep their regularly scheduled appointments, and that they have good stress-Rx. They were also less likely to feel their HCP could motivate them (62% vs. 84% and 81%, A1c 7-7.9% and A1c ≥7% respectively, p<0.05) and understand their life and challenges with T2DM (80% vs. 80% and 83%, p<0.05).

Conclusions: In addition to differing perceptions of their ability to control their T2DM and struggling with adherence behaviors, patients with A1c ≥8% appear to have difficulty relating with their HCP. Although the directionality of the poorer HCP relationships and perceptions of control is unclear, better understanding the challenges faced by patients in controlling their T2DM may aid the development of successful strategies to help patients struggling with control.

Supported By: Eli Lilly and Company (H60-US-XX02)
patient organizations, faith-based organizations, and other non-governmental organizations. The research insights led to four arenas for impactful interventions: Health promoting policies by incorporating awareness and understanding of type 2 diabetes into local policies to address the diabetes challenge and improve overall health. Urban planning by integrating health-promoting aspects such as walkability and bikeability in urban planning to increase the ability to live a healthy life. Community involvement by strengthening communities around citizens vulnerable to diabetes to build resilience, improve diabetes care and quality of life. Health system strengthening by building capacity into the local healthcare system to help vulnerable citizens to access it.

In conclusion, insights from the research have directly guided development of city-specific tailor-made interventions within four arenas.

Supported By: Novo Nordisk A/S

**840-P**

**Effectiveness of Digital Interventions for Improving Glycemic Control in Persons with Poorly Controlled Type 2 Diabetes—A Systematic Review and Meta-Regression Analysis**

MIHIRETU M. KEBEDE, HAJO ZEEB, MANUELA PETERS, THOMAS L. HEISE, CLAUDIA R. PISCHKE, Bremen, Germany

Objectives: Digital interventions may assist patients with type 2 diabetes with improving glycemic control. We aimed to synthesize effect sizes of digital interventions on glycated hemoglobin (HbA1c) levels and to identify effective features of digital interventions targeting patients with poorly controlled type 2 diabetes.

Methods and Methods: MEDLINE, ISI Web of Science and PsychInfo were searched for randomized controlled trials (RCTs) comparing the effects of digital interventions with usual care. Two reviewers independently assessed studies for eligibility and determined study quality, using the Cochrane risk of bias assessment tool. The Behavioural Change Technique Taxonomy v1 was employed to identify behavior change techniques (BCTs) employed in interventions. Mean HbA1c differences were pooled using Analysis of Covariance to adjust for baseline differences and pre-post correlations. To examine effective intervention features and to evaluate differences in effect sizes across groups, meta-regression analyses were performed.

Results: Twenty-three arms of 21 RCTs were included in the meta-analysis (n=3,378 patients, 52.6% in intervention arms). The mean HbA1c baseline differences ranged from -0.2% to 0.6%. The pooled mean HbA1c change was statistically significant (0.39 [95% CI: [-0.51, -0.26]) with substantial heterogeneity [I-squared statistic, 80.8%] and a significant HbA1c reduction was noted for web-based interventions. A baseline HbA1c level above 7.5% (p=0.04 [95% CI: [-0.81, -0.06]) and the BCTs ‘problem solving’, (β=1.30 [95% CI: [-2.05, -0.54]) and ‘self-monitoring outcomes of behavior’, (β=1.21 [95% CI: [-1.95, -0.46]) were significantly associated with reduced HbA1c levels.

Conclusions: Digital interventions appear effective for reducing HbA1c levels in patients with poorly controlled type 2 diabetes.

**841-P**

**Family Impact Module and Type 1 Diabetes**

JENNIE EILKOWITZ, MARY PAT GALLAGHER, BECKY LOIS, MORGANL, PACHECO, ANNE ZELENIUCH-JACQUOTTE, New York, NY; Manhattan, NY

Introduction: The Pediatric Quality of Life Family Impact Module (FIM) measures different domains of family functioning. Its use in type 1 diabetes (T1D) has not been widely explored. The objective of this study is to assess if baseline demographics can predict the impact of T1D on family functioning as measured by FIM score.

Methods: Parents of children with T1D completed the FIM during a medical appointment. Parents also completed the Holmes and Rahe (H and R) questionnaire as a measure of stressful life events.

Results: The sample included 133 parents. The children (13 males), had a median age of 13.6 years (range: 5.7-20.7), median age at diagnosis of 7.9 years (range: 1-15), median diagnosis duration of 5 years (range: 1-16) and median AIC of 8.4% (range: 6.5-11.4). The median FIM total score was 73.3 (range: 16-100) and impact on function was strongly correlated with a higher H and R score (r=-.94, p<.01 after excluding one outlier). Predictive characteristics were noted in some individual domains (univariate analysis, adjusting for H and R score): poorer outcomes in parent cognitive function (p=0.02) for those with a child with additional medical conditions, more communication challenges (p=0.003) for parents of males, and more worry (p=0.05) in parents with more than 1 child with T1D. Child’s gender, AIC, pump use, CGM use, age, age at diagnosis and disease duration were not significant predictors of total FIM score or FIM subscale scores.

**842-P**

**The Three 1’s of Diabetes Integration in Emerging Adulthood—Developing a Framework to Individualize Diabetes Care**

BENJAMIN MARKOWITZ, CHERYL FRITLOVE, GEETHA MUKERJI, JAMES V. LAVERY, JANET A. PARSONS, ANDREW ADVANI, Toronto, ON; Canada; Atlanta, GA

Transition of care occurs within the developmental context of emerging adulthood (18-24 years), in which diabetes self-management is challenged as an individual learns to cope with diabetes and develop their independence. With the goal of helping providers individualize support as patients begin adult care, we conducted a qualitative study with 33 emerging adults with type 1 diabetes (51% female, age 20.6±0.3 years, diabetes duration 12±1 years). Individual semi-structured interviews allowed participants to depict their lived experiences with diabetes. We employed a narrative approach to the analysis of interview transcripts and constant comparison was used to identify similarities and differences in narrative typography and thematic content. We identified that participants’ accounts of living with diabetes could be grouped into three broad categories: Ingrained (n=14), Intrusive (n=12) and Inconspicuous (n=7). We interpreted these accounts as different “lenses” through which individuals perceive their diabetes during EA. Participants conveying an Ingrained lens perceived diabetes to be comfortably settled within their daily lives and described self-confidence for management. Participants conveying an Intrusive lens perceived diabetes as disrupting their daily living and described moral sensitivity towards management (i.e., being seen as a ‘good’ or ‘bad’ self-manager). Participants conveying an Inconspicuous lens told stories that demonstrated their efforts to minimize their diabetes and described disregard for management. HbA1c levels were lower in participants conveying an Ingrained lens (HbA1c, %) and Inconspicuous (8.4±0.3). Although movement between these domains may be fluid, mixed or incomplete, this framework provides a heuristic strategy to recognize emerging adults’ varying views of their diabetes and presents opportunities for individualizing care accordingly.

Supported By: RDV Foundation; St. Michael’s Hospital Foundation; Ontario Ministry of Health and Long-Term Care

**843-P**

**Identifying Recommendations of Health Care Providers (HCP) for Developing an Evidence-Based Reproductive Health (RH) Educational Intervention for Adolescent and Young Adult (AYA) Males with T1D**

ANDREA F.R. FISCHL, INGRID LIBMAN, DANA L. ROFEY, DENISE CHARRON-PROCHownik, Pittsburgh, PA

Approximately half of males with T1D report RH complications (e.g., erectile dysfunction, decreased libido, orgasmic dysfunction) as early as 25 years old and/or 10 years after diagnosis. Tight glycemic control can prevent or delay complications, including those related to RH. Yet these sensitive topics are rarely discussed by HCPs. The purpose of this study was to collect qualitative data through a focus group conference call with 6 HCPs about their experiences caring for AYA males with T1D, and their perceptions of the need and recommendations for developing an evidence-based RH educational intervention. A semi-structured discussion guide was used to elicit responses about providing care for this population, experience with managing male RH complications, and their comfort talking to male teens about diabetes and sexual health. Responses were recorded and transcribed verbatim, and analyzed to identify major themes, using a qualitative descriptive method with 2 researchers discussing themes and reaching agreement. The 6 HCPs were 2 female pediatric diabetologists, 1 male pediatric diabetologist, 2 male adult diabetologists, and a male certified diabetes nurse educator. Following discussion, consensus was reached by all participants that RH was understudied and education was needed in this population. Major themes that emerged included: "differences in diabetes risk in the offspring," "association of the risky behaviors associated with non-adherence in diabetes self-management," “sex and diabetes” and “professional responsibility and obligation to initiate discussion,” and age to introduce these topics.”

**PSYCHOSOCIAL, BEHAVIORAL MEDICINE**

ADA-Supported Research
Moderated Poster Discussion

**A219**
In conclusion, these HCP recommendations will inform the development of a RH program for AYA males with T1D. These suggestions and issues could impact the HCP’s ability to effectively advise and educate AYA males about reproductive/sexual health and diabetes.

484-P

A Content Analysis of Text Messages in a Type 1 Diabetes Peer Mentoring Program—The Importance of Shared Interests

ASHBY F. WALKER, CATHRYN JOHNSON, CLAUDIA ANEZ-ZABALA, SARAH R. DORRIEL, MICHAEL J. HALLER, MATTHEW J. GURKA, BRITANY S. BRUGGEMAN, DANIELLE GUPTA, MARK A. ATKINSON, ILYSSA SCHATZ, DESMOND SCHATZ, Gainesville, FL; Atlanta, GA; Decatur, GA

A paucity of research exists regarding the feasibility of utilizing personalized, live-texting as outreach to improve health outcomes for low-income teenagers with type 1 diabetes (T1D). A peer mentoring program pairing college students with T1D with publicly insured teens ages 11-17 with T1D (gender matched) was piloted with the aim of improving outcomes for both groups (n=88; 44 control and 44 treatment). The program involved social events, clinical visits, automated daily texts for blood glucose monitoring (BGM), and weekly text exchanges. For consistency, mentors were trained in protocols for texts using a technique of reciprocal sharing and limited to one text exchange with their mentee a week at a time of day agreed on by parents. Mentors, mentees and parents were aware that all texts were monitored by study staff through IRB-approved processes. A content analysis of all texts for a 12-week period was conducted (47,475 words) using six coders with schemata that included presence/absence variables (e.g., did the mentor prompt for BG readings), numeric variables (word counts), and categorical variables (major themes discussed). Texts included poignant examples of uninhibited sharing about daily life and excellent coaching by mentors. However, pairs that talked about a shared common interest outside of T1D used far more words about diabetes-specific and non-specific topics both were athletes, both engaged drawing, shared an ethnic identity, etc.). Mean word use for pairs with a common interest was 2,902 compared to 1,537 with no common interest (p=.01; test). For mentors, as word use increased in texts there was a greater improvement in HbA1c (r = .54, p=.03, Pearson’s correlation). This pilot study shows the feasibility of using texting in peer mentoring programs and reiterates the importance of finding common ground beyond T1D to facilitate rapport building. Additional efforts are needed to better explicate the role of shared interests in outcomes for peer mentoring programs.

Supported By: Jake Center for Health Research

485-P

Comparing Perceptions of Concerns Regarding Complications Including Reproductive Health (RH) in Male and Female Adolescents and Young Adults (AYA) with T1D

ANDRE K. SMITH, DENISE CHARRON-PUCHOWNIK, SUSAN M. SEREKA, DANA L. ROYER, DOROTHY J. BECKER, JESSICA FINNEY, ANA M. DIAZ, INGRID LIBMAN, Pittsburgh, PA

Tight glycemic control decreases risks of complications. Male and female AYA with T1D are vulnerable to poor glycemic control resulting in retinopathy (RET), nephropathy, nephropathy, high blood pressure (HBP), and RH complications. About half of males with T1D report RH complications (e.g., erectile dysfunction) as early as 25 years and up to 10% of women with T1D have pregnancy-related complications; however, these topics are rarely discussed.

Purpose: To describe and compare concerns of diabetes-related complications, including adverse RH outcomes among male and female AYA with T1D.

Methods: A diabetes transition care program for AYA with T1D at an academic children’s hospital provides care and small group discussion-education sessions on relevant topics (e.g., RH with diabetes, complications/prevention, risk behavior, self-care). Participants were given a survey prior to the program to gauge perceptions on T1D complications. Both female (n=19) and male (n=23) participants (aged 17-22 years) ranked concerns for complications from 1 (most) to 5 (least). Mann-Whitney U-tests were used to compare perceptions of concerns regarding complications from 1 (most) to 5 (least). A significant difference between genders was HBP (p<.02), where males tended to report greater concern.

Conclusion: Retinopathy was an overall major concern. Gender differences in concerns were found for only HBP. No males ranked RH complications as a major concern. It is imperative to raise awareness and discuss concerns during adolescence. Initiating discussions with health professionals can empower AYA with T1D to maintain healthy lifestyles and prevent complications including RH.

486-P

Examination of Accuracy of Self-Reported Blood Glucose Using mHealth Data Collection

JENNIFER WARNICK, SARAH C. WESTEN, ANASTASIA ALBANESE-O’NEILL, DESMOND SCHATZ, MICHAEL J. HALLER, DAVID JANICKE, Gainesville, FL

Introduction: Daily self-monitoring of blood glucose (SMBG) is essential for type 1 diabetes (T1D) management. Adherence to SMBG is often suboptimal during adolescence. SMBG paper diaries are often inaccurate compared to glucometer readings. The current study aimed to compare self-reported SMBG values gathered using ecological momentary assessment via smartphones to glucometer readings.

Methods: Youth (n=54, 11-21 years, 59.3% male) with T1D received 3 text messages/day for 10 consecutive days containing REDCap surveys inquiring to SMBG values. SMBG values from glucometers were obtained during the same period. Based on a previously developed system, paired values were compared and categorized as accurate or discrepant. A discrepancy was categorized as: omission (i.e., glucometer reading with no self-reported SMBG value), addition (i.e., self-reported SMBG value with no glucometer reading), alteration (i.e., self-reported SMBG value different by >10 mg/dL from glucometer value), or digit transformation (i.e., 184 instead of 148).

Self-reported values were categorized further to reflect whether patients reported a more clinically favorable or unfavorable profile.

Results: A significant positive correlation was found between glucometer and self-reported SMBG values for all matched pairs (p=.628, p<.001). Out of 817 pairings, 39.3% of the self-reported values were congruent to glucometer readings and 60.7% were discrepant. Of the discrepant, 45% were alterations, 40.6% were additions, 13% were omissions, and 0.1% were digit transformations. Also, 54.5% of self-reported SMBG appeared clinically favorable, while 45.5% appeared clinically unfavorable.

Conclusions: These findings are consistent with previous studies comparing paper SMBG diaries to glucometers in a pediatric population. Self-reported mHealth data is likely to produce discrepant SMBG values compared to glucometers. Providers are urged to use objective blood glucose devices for clinical decisions.

Supported By: University of Florida

487-P

Poor Adherence in Adolescents with Type 1 Diabetes Associated with Distress, Fear of Hypoglycemia, and Executive Functioning

SARAH C. WESTEN, JENNIFER WARNICK, MINA ENTESARI, ANASTASIA ALBANESE-O’NEILL, DESMOND SCHATZ, MICHAEL J. HALLER, DAVID M. JANICKE, Gainesville, FL

Introduction: T1D poses unique challenges to adherence-related behavior due to complex treatment regimens. This study aimed to determine prevalence rates of adherence in adolescents on multiple daily injections (MDI) or subcutaneous insulin infusion (CSI). Additional aims included determination of whether adherence correlated to HbA1c and whether psychological factors predicted adherence.

Methods: Self-monitoring of blood glucose (SMBG) and insulin delivery data were downloaded for the previous 30 days. DISTress was measured using the Problem Areas in Diabetes-Teen Version, the Blood Glucose Monitoring Communication Questionnaire, and the Barriers to Diabetes Adherence Survey. The Hypoglycemia Fear Survey and Behavior Rating of Executive Function were administered. Bivariate correlations and hierarchical regressions were used to determine how adherence related to HbA1c and the predictive value of psychological factors. Continuous glucose monitor (CGM) use was considered as a covariate.

Results: Adolescents (N=81; 41 on MDI and 40 on CSI) aged 11 to 17 years completed the study. The mean HbA1c was 8.74% (SD=1.74%). Daily, <7% of participants engaged in SMBG ≥4 times; <7% engaged in carbohydrate entry ≥3 times, and <20% engaged in bolus delivery ≥3 times. Hypoglycemia readings were followed by a correction bolus in 58% of cases. HbA1c was negatively correlated with several adherence domains: frequency of SMBG (r=-0.465, p<.01), carbohydrate entry (r=-0.511, p<.01), and bolus insulin delivery (r=-0.522, p<.01). Distress and fear of hypoglycemia predicted adherence to correction bolusing for hypoglycemia (r=-0.237, p<.05) in a model with child age, gender, and executive functioning.

Conclusions: Findings suggest adolescents do not adequately adhere to treatment for T1D. The use of diabetes treatment technology is helpful to measure specific domains of adherence and clarify relationships with psychological factors.

Supported By: American Psychological Association

488-P

mHealth Data Collection
What Is Health-Related Quality of Life? Perspectives from Diabetes Care Providers
VIENA T. CAO, SAHAR S. ESHTEHARDI, BRETT M. MCKINNEY, BARBARA ANDERSON, DAVID G. MARRERO, DEBBIE THOMPSON, MARISA E. HILLIARD, Houston, TX, INDIANAPOLIS, IN, Charlottesville, VA, Tucson, AZ

Background: While health-related quality of life (HRQoL) is gaining recognition as an important patient-reported outcome, little is known about how diabetes care providers define or apply HRQoL in practice. The purpose of this study was to identify how diabetes care providers conceptualize HRQoL for youth and adults with type 1 diabetes (T1D) to help guide efforts to more routinely assess and intervene to improve HRQoL.

Methods: As part of a larger qualitative study on T1D-specific HRQoL, semi-structured qualitative interviews were conducted with 8 diabetes care providers (5 pediatric providers, 3 adult providers, 62.5% male) via focus groups or individually. Sessions were audio-recorded, transcribed, and coded to derive common themes.

Results: Providers identified three key components of T1D-specific HRQoL: 1) their patients’ day-to-day functioning, including the ability to engage in everyday activities and its impact on their emotional well-being; 2) their patients’ medical management, including diabetes self-management behaviors and presence of complications and hyper/glycemia; and 3) the impact of T1D on their patients’ personal relationships, including the impact on the HRQoL of their parents/partners.

Conclusion: Providers described three aspects of T1D-specific HRQoL: everyday functioning, medical considerations, and interpersonal relationships. This extends the HRQoL literature from other chronic condition populations, which has not emphasized provider perceptions of HRQoL, has primarily identified medical domains such as disease-specific symptoms/complications, and provides little understanding of HRQoL of other family members. Together with findings about patient/family perspectives on HRQoL from the larger study, the current findings about how diabetes care providers conceptualize diabetes-specific HRQoL are necessary to help guide clinical processes to routinely assess and enhance HRQoL across the lifespan.

Supported By: The Leona M. and Harry B. Helmsley Charitable Trust

Factors Affecting Long-Term Healthy Behaviors and Posttraumatic Growth in Type 2 Diabetes Patients
AYAKO KAYANO, MASAHIRO YAMAZAKI, KANAKO TAKU, RYOSUKE SAKAI, NAOKO HIGO, MAI ASANO, TOYOUSHI HOSOKAWA, MASATOSHI KAWASE, MIHAKI FUKUI, Kyoto, Japan, Rochester, MN

Background/Purpose: Constant self-management is important for type 2 diabetes patients to improve or maintain their quality of life, however it can become difficult and burdensome. The purpose of the current study is to quantitatively investigate the mechanisms of psychological adaption to a type 2 diabetes diagnosis and the factors affecting long-term healthy behaviors by referring to a theoretical framework of Posttraumatic Growth (PTG), that is, personal growth resulting from struggle with trauma.

Methods: A series of semi-structured interviews were conducted with adult patients (N = 10) who were diagnosed with type 2 diabetes over two years prior, maintaining an HbA1c of under 8% stable over 6-months, and showed a relatively higher level of PTG in a screening test using the extended version of the PTG Inventory.

Results: Interviews were analyzed by the Grounded Theory Approach. Three main mechanisms were identified. (1) Some were able to continue healthy behaviors because they experienced PTG as a result of single major life event that occurred prior to diagnosis. (2) Some were able to continue healthy behaviors because they experienced PTG as a result of a number of minor but stressful life events that occurred in succession prior to diagnosis. (3) Others were able to continue healthy behaviors because they experienced PTG directly as a result of the diagnosis of diabetes. Overall, patients included in the current analyses were not overly conscious of their diagnosis or treatment in their daily lives, and did not seem to struggle with identity conflicts relating to their diagnosis.

Conclusion: Current study identified three paths leading to healthy behaviors. Regardless of the triggering events, PTG experiences seem to transform cognitive processes and increase stress tolerance, resiliency, and perhaps purpose in life and a sense of identity, and thus enable them to maintain healthy behaviors. Future study should explore the paths among patients who have not experienced PTG.

Evaluation of a Web-Based Tool for Parents of Teens with Type 1 Diabetes
ROBIN WHITTEMORE, JULIA L. COLEMAN, ROBERTA DELVY, BERNET KATO, JAMES A. AMBROSOULI, MICHAEL P. MAURAO, REBEKAH ZINCAYIDE, LISA MARCEAU, West Haven, CT, Watertown, MA

Parents of teens with type 1 diabetes (T1D) report challenges in maintaining involvement with diabetes care while supporting teen autonomy. We developed a web-based tool to support parents in this transition—Type 1 Teamwork—that provides interactive content and video vignettes of real families on challenges and strategies to transition T1D care from parent to teen. The purpose of this study was to determine the reach (demographic characteristics), participation (web usage and engagement) and short-term effects (parenting stress, perceived stress, parental support for teen autonomy, family conflict, teen A1C) of Type 1 Teamwork. Parents of teens with T1D (11-16 years) were randomized to Type 1 Teamwork (n=81) or a control group (n=81). Parents were 45.6 (±5.3) years of age, 98% female, 91% white, 91% married/partnered, 51% high income, 36% with elevated depressive symptoms, and 40% with elevated anxiety symptoms. Teens had a mean A1C of 7.9 (±1.2), T1D duration of 5.08 (±3.62) years, with 75% using a pump, 69% using a CGM, and 39% reporting 20 or more episodes of hypoglycemia in the previous 3 months. There were no significant differences between groups on baseline characteristics. Eighty-two percent (n=133) of participants completed 3-month data collection. Parents in the Type 1 Teamwork group who did not access the tool (n=8) were excluded from the comparative analyses. Type 1 Teamwork was accessed a total of 453 times and had 6,614 total pages viewed, with an average of 15 pages and 11 minutes per visit. There was less frequent parenting emotional distress (p=0.04) and trends for less family conflict (p=0.14) in the Type 1 Teamwork group, with no short-term effect on perceived stress, parental support for autonomy, or teen A1C in change scores over 3 months. Ongoing usage of Type 1 Teamwork may further enhance outcomes in parents of teens with T1D, which we will evaluate at 6 months. More research is needed to engage lower income families in the use of websites to support parent-teen teamwork in T1D.

Supported By: National Institute of Diabetes and Digestive and Kidney Diseases
852-P  
**The Influence of Daily Stress on Glycemic Control and Mortality in Adults with Diabetes**

REBEKAH J. WALKER, EMMA GARACCI, JENNIFER A. CAMPBELL, LEONARD E. EGEDE, Milwaukee, WI

**Background:** Daily stress may compound the burden of diabetes. This analysis investigated whether frequency or severity of stress had an influence on glycemic control (HbA1c) and mortality in adults with diabetes.

**Methods:** Data from the second and third wave of the national longitudinal survey of Midlife Development in the United States (MIDUS), conducted between 1995 and 2014, was used. A total of 141 adults with diagnosed and undiagnosed diabetes, based on HbA1c and self-report of diagnosis, completed the national study of daily experiences (NSDE) project during which questions were asked about daily stress type, frequency, and impact for eight consecutive nights. General linear models investigated the relationship between stress and HbA1c. Cox proportional hazard models estimated hazard ratios using national death index information linked to MIDUS data.

**Results:** On average, this population of adults with diabetes reported 3.1 days with a stressor and 3.9 stressors in an 8-day period. While 21.9% reported only one stressor type, 72.3% reported more than one stressor type. No significant relationships existed between number of days with stressor, average number of stressors, or number of stressor types. Average physical symptom severity reported in relation to stressful events was negatively associated with HbA1c (β = -0.20, p = 0.04). The average stressor severity and average stressor negative affect were both significantly associated with mortality (HR = 0.45, p = 0.04 and HR = 0.17, p = 0.03, respectively).

**Conclusions:** Daily stress may influence outcomes for adults with diabetes; in particular, severity of stressors experienced, severity of physical symptoms related to stressors, and negative affect (negative emotions and poor self-image) related to stressors. Interventions addressing psychosocial factors, such as daily stress, in individuals with diabetes may need to focus on helping individuals mitigate the impact of stress rather than decrease the amount of stress in their lives.

853-P  
**Glycemic Factors Related to Depression in Adults with Type 1 Diabetes**

IFEOMA EGBUONU, PAULA M. TREF, CHERYL A. ROE, RUTH S. WEINSTOCK, Syracuse, NY

**Objective:** To compare glycemic factors (home glucose monitoring, glucose variability, A1c) in adults with type 1 diabetes (T1D) with probable depression to those without depression in a real world setting.

**Methods:** Adults with T1D at our diabetes center are routinely screened for depression with the PHQ-2. If the PHQ2 score is ≥3, PHQ9 is completed. Medical records were reviewed including device downloads for adults with PHQ2 scores >10 (“depressed”) and age-matched “not depressed” (PHQ2 scores ≤3). Patients with T1D duration <1 year, GFR ≤30 mL/min/1.73m2, hemoglobinopathy or dementia were excluded.

**Results:** Of 1272 adults screened, 83(1.4%) were depressed, and compared to an age-selected group of 171 non-depressed T1D adults (age range: 18-72 years, 86% white, 8% black, 98% non-Hispanic, 42% Medicaid). Depressed (mean [SD]) PHQ9 score 16.8 (4.3) did not differ from non-depressed on age (41.7 [15.6] vs. 41.8 [15.7] years), BMI [29.3 [8.8] vs. 28.9 [6.2] kg/m²], T1D duration [21.2 [13.8] vs. 22.0 [15.0] years], or % male [42.2 [vs. 40.9]. Meter downloads were available for 215/254 patients (74% of depressed, 96% of non-depressed). The depressed group had higher A1c [9.6% (2.3) vs. 8.6% (1.8), p<0.001], and fewer glucose tests/day (2.8 [2.3] vs. 3.6 [2.5], p=0.048) based on meter downloads. Prior work found that depression did not relate to self-reported glucose monitoring in T1D adults. The groups did not differ on meter %, coefficient of variation (CV; mean 42%) or % with hypoglycemia (glucose reading <54 mg/dL). Continuous glucose monitoring (CGM) was used by 38 patients; CGM % CV also was not different in those depressed (35 [6.2], n=5) vs. non-depressed (36.0 [8.0], n=33). The depressed group using CGM had lower A1c, suggesting that CGM use should be withheld in the presence of depression. The small number of patients using CGM is a limitation.

**Conclusion:** Adults with T1D and probable depression had higher A1c, less meter use, fewer glucose readings/day, but no difference in glucose variability (± CV) or hypoglycemia (<54 mg/dL).

854-P  
**Correlates of Perceived Stress in Parents of Teens with Type 1 Diabetes**

ROBIN WHITTEMORE, ROBERTA DEUVY, JULIA L. COLEMAN, BERNET KATO, JAMES A. AMBROSOLI, MICHAEL P. MAURAD, REBEKAH ZINCAVAGE, LISA MARESEAU, West Haven, CT; Watertown, MA

Parents of teens with type 1 diabetes (T1D) are responsible for a labor-intensive and complicated daily regimen that has been described as overwhelming and requiring constant vigilance. Parents report high levels of stress, particularly during the adolescent transition. The primary aim of this study was to identify demographic (parent/child age, gender, race/ethnicity, income, marital status), clinical (T1D duration, pump use, CGM use, epi- sodes of hypoglycemia, other health diagnoses) and psychosocial factors (depressive symptoms, family conflict, childhood-illness parenting stress, teen autonomy) associated with perceived stress in parents of teens with T1D. This was a secondary analysis of baseline data from parents (n=162) of teens with T1D (11-16 years) who were enrolled in a study to evaluate a web-based tool to help with the transition of diabetes care. Bivariate correlates of perceived stress were included in a multivariate model analysis. Parents were 45.6 (±5.3) years of age, 98% female, 91% white, 91% married/partnered, 51% high income, 36% with elevated depressive symptoms, and 40% with elevated anxiety symptoms. Teens had a mean A1C of 7.9 (±2.1), 5.08 (±3.62) years duration of diabetes, with 75% using an insulin pump, 69% using a CGM, and 39% reporting 20 or more episodes of hypoglycemia in the previous 3 months. Significant bivariate demographic, clinical, and psychosocial correlates were included in the model, in a stepwise procedure. Multivariate correlates of perceived stress were parent age, teen T1D duration, other teen health diagnosis (R²=0.13, p<0.01), family conflict and childhood-illness parenting stress (R² change=.30, p<.01), and parent depression (R² change=.18, p<.01), explaining 62% of the variance. Parents of teens with T1D experience high stress and may need additional support to prevent and/or decrease family conflict, childhood-illness parenting stress, and depressive symptoms. Parent stress has health implications not only for parents, but also teens with T1D.

**Supported By:** National Institute of Diabetes and Digestive and Kidney Diseases
Exercise is a cornerstone of type 2 diabetes (T2D) treatment, but most people with T2D are sedentary. We identified a novel behavioral barrier to exercise in women with T2D compared to nondiabetic women — greater effort for adults across a range of exercise intensities, even when controlling for fitness. As T2D decreases fitness more in women than men, we also hypothesized sex would modify this association. We analyzed secondary data from past sedentary, overweight research participants with and without T2D who were free of cardiopulmonary comorbidities. During graded exercise tests to assess fitness (VO₂peak), we repeatedly measured objective effort (heart rate (HR)) and subjective effort ( Borg Rating of Perceived Exertion (RPE)). We plotted the rise of RPE and HR, respectively, against increases in relative work rate (%VO₂peak; VO₂ at work rate divided by VO₂peak) at lower intensities below anaerobic threshold (AT) and higher intensities above AT. Adults with T2D (n=57) had similar age and adiposity as those without T2D (n=56), but had lower VO₂peak: 20.7±4.5 vs. 24.5±6.6 ml/kg/min (p<0.05). Below AT, people with T2D had a steeper rise in RPE for each unit increase in %VO₂peak than those without T2D (p=0.0029), and this finding was more pronounced in men than women (p=0.004). T2D status did not influence the association of %VO₂peak and RPE above AT, or the association of HR and %VO₂peak either below or above AT. People with T2D have significantly greater RPE during lower intensity exercise below AT as compared to people without T2D. This finding was not explained by fitness differences and, counter to our hypothesis, was more significant in men. We found no group differences in RPE at higher intensity exercise where physiological inputs tend to dominate behavioral predictors of effort. Future work should further characterize sex-specific mechanisms of exercise effort for people with T2D.

Supported By: National Institutes of Health

Effects of Mindfulness-Based Stress Reduction on Insulin-Treated Diabetes

RAQUEL REIN, MEGHAN SEARL, SHREYA BHANDARI, KATHRYN E. COTE, ISRA HASHMI, KAYLA L. DEL VALLE, MARIE E. MCDONNELL, Bostons MA

Patients with type 1 (T1D) and type 2 diabetes (T2D) on insulin experience significant diabetes related distress (DD) which is known to negatively impact overall health and ability to self-manage the disease. Mindfulness Based Stress Reduction (MBSR) is an 8-week in-person group-taught program that has been shown to be effective in improving outcomes in chronic diseases. However, MBSR research in diabetes has been limited and has not included complex diabetes. We hypothesized that MBSR would lower DD and improve glycemic control in patients with uncontrolled insulin-treated diabetes. We conducted a nonrandomized pilot feasibility study of MBSR in insulin-treated patients with A1c≥8.6% and regimen-related distress (r=1.2, p=0.01) and regimen-related distress (r=1.2, p=0.004). At 6 months, the mean A1c reduction was -0.4% +/- 0.9%. The reduction in PAID score correlated with A1c reduction (r=0.5).

In conclusion, uncontrolled insulin treated diabetes patients who participated in MBSR experienced a sustainable improvement in emotional and regimen-related distress which was accompanied by lower A1c. Results suggest the need for a large clinical trial designed to optimize accessibility to a broader population of patients and to test the cost-effectiveness of this nonpharmacologic intervention.

Materials and methods: In the Appalachian region of rural southeastern Ohio, diabetes rates are more than double the national average (19.9% vs. 9.4%). Here, diabetes patients are more likely to have a delayed diagnosis, microvascular complications, depression, and lower empowerment. Further, nearly a third of residents are living below the poverty line and suffer from higher unemployment rates, lower educational achievement, poorer health, food insecurity, and lower access to care. Thus, strategies that complement standard diabetes care are critically important to alleviate the burden of complications, reduce health disparities, and improve quality of life. We designed the Diabetes Navigation Program to improve health outcomes and address social determinants of health by expanding access to care and enhancing care coordination via nurse navigators. To date, 47 adult patients with type 2 diabetes have completed the program (94% white, 66% female, 61±16 years old, A1c=9.0±2.7%, 12±8 years duration). At baseline, 24% of patients reported moderately severe to severe depression as measured via the PHQ-9, and 53% reported moderate to serious diabetes distress as measured via the PAID-5. Patients showed a significant improvement in A1C from baseline to 6-month follow-up (mean change: -1.2 points, t=2.23, p=0.017); however, no improvements were observed in depressive symptoms (n=1.37, p=0.199) or diabetes distress (n=2.92, p=0.033). The nurse navigator provided increased insurance coverage (59%), food stamps (50%) and emergency food boxes (16%), permanent or temporary housing (23%), diabetes education (21%), reduced hospital bills (14%), diabetes medication (14%), and emotional support (71%). These data are promising though more data are necessary to evaluate the clinical effectiveness. The next step is to design a randomized controlled trial to test the efficacy of navigation as compared to usual care. In the long term, this work has the potential to reduce health disparities and improve access to care for in Appalachian Ohio.

Supported By: Health Resources and Services Administration (D04RH28409)

A Nurse-Led Diabetes Navigation Program for Rural Appalachian Ohio

ELIZABETH A. BEVERLY, EMILY H. GUSEMAN, KARIE A. COOK, MELISSA STANDLEY, Athens, OH

In the Appalachian region of rural southeastern Ohio, diabetes rates are more than double the national average (19.9% vs. 9.4%). Here, diabetes patients are more likely to have a delayed diagnosis, microvascular complications, depression, and lower empowerment. Further, nearly a third of residents are living below the poverty line and suffer from higher unemployment rates, lower educational achievement, poorer health, food insecurity, and lower access to care. Thus, strategies that complement standard diabetes care are critically important to alleviate the burden of complications, reduce health disparities, and improve quality of life. We designed the Diabetes Navigation Program to improve health outcomes and address social determinants of health by expanding access to care and enhancing care coordination via nurse navigators. To date, 47 adult patients with type 2 diabetes have completed the program (94% white, 66% female, 61±16 years old, A1c=9.0±2.7%, 12±8 years duration). At baseline, 24% of patients reported moderately severe to severe depression as measured via the PHQ-9, and 53% reported moderate to serious diabetes distress as measured via the PAID-5. Patients showed a significant improvement in A1C from baseline to 6-month follow-up (mean change: -1.2 points, t=2.23, p=0.017); however, no improvements were observed in depressive symptoms (n=1.37, p=0.199) or diabetes distress (n=2.92, p=0.033). The nurse navigator provided increased insurance coverage (59%), food stamps (50%) and emergency food boxes (16%), permanent or temporary housing (23%), diabetes education (21%), reduced hospital bills (14%), diabetes medication (14%), and emotional support (71%). These data are promising though more data are necessary to evaluate the clinical effectiveness. The next step is to design a randomized controlled trial to test the efficacy of navigation as compared to usual care. In the long term, this work has the potential to reduce health disparities and improve access to care for in Appalachian Ohio.

Supported By: Health Resources and Services Administration (D04RH28409)
861-P  
Dispelling Misperceptions—Family Satisfaction with Behavioral Health Screening  
DANNY C. DUKE, HARPREET NAGRA, MELINDA JONES, MORGAN BOLEN, MICHAEL A. HARRIS, Portland, OR

Objectives: The ADA has recommended routine behavioral health screening of youth with T1D given the associations among psychological factors (e.g., depression and anxiety), the skills necessary to manage diabetes (executive functioning), and adherence and health outcomes. Anecdotally, concerns of healthcare providers and staff have included stigma, inconveniency, time, and/or unacceptable burden. However, family acceptance of behavioral health screening has not been systematically assessed.

Methods: After administering a screening protocol for youth with T1D, we administered a brief patient satisfaction questionnaire. The screening protocol included the PHQ-9, GAD-7, DREFS-SF, and the DSM-5P-SF. During this pilot, 57 youth (11-18 years), and 84 parents completed the screenings. Youth and parents completed the brief quality improvement survey after completing the behavioral health screening. Youth and parents responded to questions using a five-point scale from “strongly agree” to “strongly disagree.”

Results: Completing questionnaires was an inconvenience to 4.8% of parents and 1.8% of children. The information from questionnaires is important for diabetes care providers to 98.8% of parents and 94.6% of children. Completing the questionnaire was a burden to me or my family to 8.1% of parents and 7.1% of children. The questionnaires were too long to 2.4% of parents and 1.8% of children. The questionnaire about how well diabetes has been managed was helpful to 98.8% of parents and 96.4% of children.

Conclusions: Concerns regarding family satisfaction with behavioral health screening of youth with T1D were unfounded. Behavioral health screening was very acceptable to the vast majority of youth and parents with no indication that there was stigma associated with behavioral health issues.
Does Gender Moderate the Relations between Shared Responsibility and Health Outcomes among Adolescents with T1D?

HIBA ABULJARAD, DEHAN M. SHEREKA, SUSAN M. COHEN, VICKI HELGESON, Pittsburgh, PA

Shared responsibility (SR) where both parents and adolescents are involved in diabetes management is optimal for reducing psychological distress and improving diabetes outcomes. Few studies examined whether gender moderates the relations between SR and health outcomes. This study examined whether gender moderates the relations of SR to distress and diabetes outcomes during the transition into adolescence. A secondary analysis of longitudinal study of 132 adolescents with T1D and their parents was conducted. Adolescents were 10 to 14 years, 72 girls and 60 boys. All measures were taken annually for 5 years. Both reported on SR. Adolescents reported on distress (depressive symptoms, anxiety, and anger) and self-care. HAIC was obtained at the clinic visit. Linear mixed models were used to assess if gender moderates the relations between SR and health outcomes.

Results: Concurrent analyses showed that gender moderated the relation between parent-reported SR and HAIC (p=0.07) and child-reported SR and anger (p=0.48). At early adolescence, parent-reported SR was associated with lower HAIC for girls but higher HAIC for boys. For middle-stage adolescence, SR was associated with higher HAIC for girls but lower HAIC for boys. For older adolescents, SR was associated with lower HAIC for boys but unrelated to HAIC for girls. Among young and older adolescents, child-reported SR was associated with less anger for boys but unrelated to anger for girls. At middle-stage adolescence, SR was associated with less anger for girls but more anger for boys.

Conclusion: gender moderated the relations between SR and some aspects of health outcomes during transition adolescence in different patterns. SR was associated with better glycemic control among young girls and older boys, and was associated with less anger among boys in general. Healthcare providers need to consider adolescent’s gender when recommending parental involvement in diabetes management for better health outcomes.

Supported By: National Institutes of Health (R01 DK0586) Pediatric Clinical and Translational Research Center at Children’s Hospital (SM01 RR00084)

Psychological Distress Mediates the Association between Poor Sleep Quality and Prediabetes

LILLI BIRMINGHAM, AL

Background: Evidence indicates that poor sleep quality increases risk for prediabetes. Psychological distress may be a potential mechanism through which poor sleep quality affects glucose metabolism. Sleep, prediabetes, and distress are linked to type 2 diabetes. We examined the relations between poor sleep quality and prediabetes, and tested whether psychological distress may mediate the relation between poor sleep quality and prediabetes. A second analysis of longitudinal study of 132 adolescents with T1D and their parents was conducted. Adolescents were 10 to 14 years, 72 girls and 60 boys. All measures were taken annually for 5 years. Both reported on SR. Adolescents reported on distress (depressive symptoms, anxiety, and anger) and self-care. HAIC was obtained at the clinic visit. Linear mixed models were used to assess if gender moderates the relations between SR and health outcomes.

Results: Concurrent analyses showed that gender moderated the relation between parent-reported SR and HAIC (p=0.07) and child-reported SR and anger (p=0.48). At early adolescence, parent-reported SR was associated with lower HAIC for girls but higher HAIC for boys. For middle-stage adolescence, SR was associated with higher HAIC for girls but lower HAIC for boys. For older adolescents, SR was associated with lower HAIC for boys but unrelated to HAIC for girls. Among young and older adolescents, child-reported SR was associated with less anger for boys but unrelated to anger for girls. At middle-stage adolescence, SR was associated with less anger for girls but more anger for boys.

Conclusion: gender moderated the relations between SR and some aspects of health outcomes during transition adolescence in different patterns. SR was associated with better glycemic control among young girls and older boys, and was associated with less anger among boys in general. Healthcare providers need to consider adolescent’s gender when recommending parental involvement in diabetes management for better health outcomes.

Supported By: National Institutes of Health (R01 DK0586) Pediatric Clinical and Translational Research Center at Children’s Hospital (SM01 RR00084)

Randomized Trial of a Tailored Cognitive Behavioral Intervention in Type 2 Diabetes with Comorbid Depressive and/or Distress Symptoms—Twelve-Month Outcomes from COMRADE

DOYLE M. CUMMINGS, LESLEY LUTES, SHIVA JRAJ PATIL, BERTHA HAMID, MARISSA CHARRAWAY, KERRY LITTLEWOOD, ALYSSA ADAMS, CHELSEY SOLAR, SHEILA EDWARDS, FEGGY GATLIN, Greenville, NC; KELLOWNA, BC; CANADA, TAMPA, FL

Patients with type 2 diabetes (T2D) and co-morbid depressive and/or distress symptoms have poor glycemic control and worse health outcomes. This prospective randomized controlled trial evaluated the effectiveness of a 16-session tailored cognitive behavioral intervention plus lifestyle change counseling (n = 67; IG=intervention group) delivered by trained staff compared to usual care (n = 72; CG=control group), in 139 rural adult patients (mean age = 52.6 ± 9.5 years.; 72% black; BMI = 37.0 ± 9.0) with uncontrolled mean HbA1c = 9.6 ± 2.0 T2D (62% on insulin) and co-morbid depressive (PHQ-2) or distress (DSS-2) symptoms at screening in an academic primary care clinic. At baseline and at 12-month follow-up: height, weight, BP, A1c, diabetes distress (DSS-17), depressive symptoms (PHQ-9), self-care behaviors (SDSQA), empowerment (IDES), and medication adherence (ModMaaS) were measured using validated instruments. There were no differences between groups at baseline. Between group (IG vs. CG) differences at 12-months follow-up were significant for changes from baseline in diabetes-related distress (-0.83 ± 0.88 vs. -0.15 ± 0.92; p = 0.001), regimen-related distress (-1.12 ± 1.05 vs. -0.31 ± 1.22; p = 0.001), depressive symptoms (-3.39 ± 5.00 vs. -0.30 ± 0.17; p = 0.01), self-care behaviors (+1.10 ± 1.30 vs. +0.58 ± 1.45; p = 0.03), and medication adherence (+1.90 ± 2.0 vs. +0.17 ± 1.0; p = 0.02). Differences in change in IG vs. CG = 0.92 ± 1.81 vs. -0.31 ± 2.04; p = 0.06) were substantially greater in the intervention group and achieved borderline significance. There were no significant differences in glycemic response patterns by race or gender. A tailored cognitive behavioral intervention significantly improved behavioral outcomes and glycemic control in rural black and white patients with T2D and co-morbid depressive and/or distress symptoms.

Supported By: Bristol-Myers Squibb Foundation
Hypoglycemia Contributes to Increased CVD Mortality with HbA1c <6.0%
MARY RHEE, KATHERINE E. KURGANSKY, YUK-LAM HO, DAVID R. GAGNON, SRIHARAN RAGHAVAN, JASON L. VASSY, KELLY CHO, ADRIANA GONZALEZ, FARRAH N. KHAN, LISA R. STAIMEZ, CHRISTOPHER N. FORD, PETER W. WILSON, LAWRENCE S. PHILLIPS, DECATOR Q4, BOSTON, MA; DENVER, CO; ATLANTA, GA

Better diabetes control generally reduces development of complications, but those with HbA1c <6.0% have increased cardiovascular (CVD) mortality. Since the cause is unknown, we studied the potential contributions of hypoglycemia, using VA and Medicare databases. 297,263 Veterans with diabetes (ICD-9 codes and diabetes Rx) had ≥4 primary care provider (PCP) visits in 2002-2003, baseline data including age, sex, race, ethnicity, BMI, non-HDL cholesterol, systolic blood pressure (SBP), smoking, ≥1 HbA1c, ≥3 outpatient random plasma glucose (RPG) levels, follow-up through 2012, and survived at least 1 year after A1c measurement. The 40,429 with A1c <6.0% (A1c-6) had mean age 66 year, were 98% male, 16% black and 6.5% Hispanic, had BMI 31, eGFR 71, sBP 139, 81% ever smoked, 51% had CVD at baseline, 48% used sulfonylureas and 13% insulin, with mean HbA1c 5.5%, and RPG 125 mg/dl, while 50,574 with HbA1c 6.0-6.9% (A1c-6.9) had HbA1c 6.5% and RPG 141 (both p<0.001), but were otherwise clinically comparable.

In fully adjusted Cox proportional hazard models, A1c-6 had increased CVD mortality compared to A1c-6.9 (HR 1.07, p<0.001). However, within 1 year after baseline, A1c-6 also had increased frequency of both outpatient RPG <70 (8.4% vs. 6.0%, p<0.001), outpatient point of care glucose (POCG) <70 (0.34% vs. 0.29%, p=ns), and emergency visits with hypoglycemia (EDHYPO). Moreover, in Cox models including HbA1c (<6.0-6.9, -7.9-8.9, ≥9.0%), hypoglycemia measured by (i) outpatient RPG or POCG <70 predicted CVD mortality more consistently than EDHYPO.

Conclusion: Hypoglycemia-associated CVD mortality occurs in general clinical practice-especially with outpatient glucose <70 mg/dl-and increased mortality with HbA1c-6.0% may be due in part to hypoglycemia. Management should be aimed to optimize control but limit the risk of hypoglycemia.

Supported By: U.S. Department of Veterans Affairs; National Institutes of Health

Which Relationships Really Matter for Blood Glucose Control?
PATRICIA N. E. ROBERSON, MELANIE MILLER, KATHERINE M. RASPOVIC, JAVIER LA FONTAINE, FRANK FICHAM, DANE WUKICH III, Davis, CA; Dallas, TX; Tallahassee, FL

For diabetics, the mental health facets of quality of life are often comorbid with the development and progression of the disease. Compared to the general population, depressive and anxiety symptoms (D/A) are higher among diabetics. Further, several factors associated with higher D/A (e.g., obesity-promoting behaviors and neuroendocrine and inflammatory responses) cause the development of diabetes, progression of the disease, and insulin resistance. In the general population, social relationship quality is consistently linked to D/A with lower quality linked to more D/A. However, among diabetics, little is known about how social relationships are linked to D/A.

In the present study, we test how diabetic patients’ marital (n = 121), family, and friendship relationship quality (n = 160) are linked to their self-reported depressive and anxiety symptoms using a series of univariate and multivariate regression models (Table 1). Findings indicate a consistent link across relationships and A/D but especially marital and family relationships in multivariate models. These relationships are linked to patient’s quality of life and potentially subsequent physiological and behavioral factors associated with blood glucose regulation. Therefore, as practitioners alter standard care practices to improve patient’s quality of life, they should consider assessing social factors in addition to individual factors.

### Table 1. Results of the univariate linear regression models for each measure of social support. In this Table we present standardized coefficients with standard error (B(SE)), 95% confidence interval (95% CI), Standardized coefficients (Beta), probability value (p-value), variance explained (R^2), and effect size (Cohen’s d).

<table>
<thead>
<tr>
<th>Variable</th>
<th>B(SE)</th>
<th>95% CI</th>
<th>Beta</th>
<th>p-value</th>
<th>R^2</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1: Family Support</td>
<td>-13.19</td>
<td>-22.54</td>
<td>-0.19</td>
<td>0.02</td>
<td>0.00</td>
<td>0.16</td>
</tr>
<tr>
<td>Model 2: Family Strain</td>
<td>-12.20</td>
<td>-30.40</td>
<td>0.04</td>
<td>0.00</td>
<td>0.04</td>
<td>0.22</td>
</tr>
<tr>
<td>Model 3: Friend Support</td>
<td>-13.29</td>
<td>-22.51</td>
<td>-0.14</td>
<td>0.02</td>
<td>0.00</td>
<td>0.16</td>
</tr>
<tr>
<td>Model 4: Friend Strain</td>
<td>-0.24</td>
<td>-4.14</td>
<td>0.02</td>
<td>0.44</td>
<td>0.12</td>
<td>0.06</td>
</tr>
</tbody>
</table>

### Table 5: Spousal Support
- Model 5: Spousal Support | -57.28 | -106.67 | -20.03 | 0.04 | 0.17 |

### Table 6: Spousal Strain
- Model 6: Spousal Strain | 51.23 | 86.96 | 20.03 | 0.04 | 0.20 |

### Table 2. Results of the multivariate linear regression models for each measure of social support.

<table>
<thead>
<tr>
<th>Variable</th>
<th>B(SE)</th>
<th>95% CI</th>
<th>Beta</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1: Family Support</td>
<td>-13.19</td>
<td>-22.54</td>
<td>-0.19</td>
<td>0.02</td>
</tr>
<tr>
<td>Model 2: Family Strain</td>
<td>-12.20</td>
<td>-30.40</td>
<td>0.04</td>
<td>0.00</td>
</tr>
<tr>
<td>Model 3: Friend Support</td>
<td>-13.29</td>
<td>-22.51</td>
<td>-0.14</td>
<td>0.02</td>
</tr>
<tr>
<td>Model 4: Friend Strain</td>
<td>-0.24</td>
<td>-4.14</td>
<td>0.02</td>
<td>0.44</td>
</tr>
</tbody>
</table>

### Table 3: Spousal Support
- Model 5: Spousal Support | -57.28 | -106.67 | -20.03 | 0.04 |

### Table 4: Spousal Strain
- Model 6: Spousal Strain | 51.23 | 86.96 | 20.03 | 0.04 |
Building Infrastructure for Diabetes Self-Management Support in Church-Based Settings—Results of a 15-Month Cluster-Randomized Controlled Trial

Nikolas J. Koscielniak, Martha Funnell, Gretchen Piatt, Ann Arboc M.

Diabetes self-management support (DSMS) is not a covered benefit in the U.S. health system, and little is known about the infrastructure needed to provide effective DSMS in organizations without existing diabetes self-management education (DSME) programs. The Praise study is a 15-month cluster-randomized controlled trial in 9 African American (AA) churches in metro-Detroit, as a conduit to build infrastructure for DSMS in low-resource communities. From 2013-2015, Praise examined the effects of peer-led DSMS on A1C and diabetes distress (DD) at 3, 9, and 15 months. CDEs trained peer leaders (PL) (n=12) and parish nurses (PN) (n=3) on goal setting, skills development, and group facilitation. Following professionally-delivered DSME, 6 monthly DSMS groups were independently planned and facilitated by 12 PL (mean age: 61.9 years, 100% AA, 25% male), followed by an additional 6 months of ongoing support to assess the logistical feasibility of sustaining DSMS efforts. Churches (and their participants, n=94) were randomized to 3 parallel groups: 1.) PL only (n=28, 2.) PN + PL (n=38), or 3.) enhanced usual care (n=30). Over time, a significant increase in A1C (p<.03) was observed across groups overall, but not within study groups. After adjusting for multiple factors, younger age (p<.04, p<.004) and lower levels of DD (p<.04) were associated with improvements in A1C over time, while insulin use (p<.032) was associated with increases in A1C. A marked improvement in DD was observed (p<.04) overall. PL only (p<.003), PN+PL (p<.01), and A1C (p=0.02) were significantly associated with improvements in DD. Results suggest DD is a significant indicator of improvement in A1C levels. DD levels also improved following a faith community-based DSME intervention and were sustained by using the PL and PN DSMS infrastructure of the church. Opportunities to expand the DSMS infrastructure beyond churches and into other community organizations is needed.

Supported By: Bristol-Myers Squibb Foundation

873-P The Emotional Side of Diabetes and Glycemic Control in a Brazilian Sample of Adults with Type 1 Diabetes

Mónica S.V.M. Silveira, Marie C. Parisi, Sr., Kristine Rufer, Arnaldo Moura Neto, Linda M. Siminerio, Andrei C. Spisito, Martha Funnell, Elizabeth J. Pavin, Sr., Lawrence Fisher, Campinas, Brazil, Pittsburgh, PA, Ann Arbor, MI, San Francisco, CA

Adults with type 1 diabetes (T1D) have a higher risk of developing depression symptoms during their lives and new research shows that over 40% of T1Ds experience elevated diabetes-related distress (DD). Psychosocial assessment is recommended as a critical part of patient-centered care in order to promote better diabetes outcomes and psychosocial well-being. The goals of this study were to document the prevalence of and relationships among Major Depressive Disorder (MDD), depression symptoms and DD, and to determine the linkage each of these measures with glycemic control in a Brazilian sample of adults with T1D at The State University of Campinas, Brazil. In a cross-sectional study, 70 T1D adults were evaluated. Inclusion criteria were age ≥18 and diagnosis of T1D ≥6 months. Exclusion criteria were cognitive impairment, history of major psychiatric disorders (e.g., schizophrenia, drug addiction, dementia), and severe diabetes-related complications (blindness, need for hemodialysis, limb amputations, stroke). Diagnoses of MDD were made using DSM-5 criteria. Depression symptoms were evaluated by the depression subscale of the Hospital Anxiety and Depression scale (HAD-D). The Diabetes Distress Scale (DDS) assessed DD. Metabolic control was evaluated by HbA1c. The latest lipid panel results were recorded and BMI was calculated. Number of complications was obtained from medical records. Forty percent of T1D were male, mean age 31±8.8, mean number of complications was 1 ±1.2, and mean HbA1c was 10.0%±2%. Frequency of MDD was 30.0% and 35.7%, reported high depression symptoms. Fifty-two percent reported high DD. Only DD and depression symptoms were each significantly and positively associated with HbA1C (p < .05). This study shows that several measures that reflect the emotional side of diabetes are related to glycemic control. They emphasize the need to incorporate the emotional side of diabetes into strategies of care for adults with T1D.

872-P Raising a Child with Type 1 Diabetes and Autism—Using Social Media to Identify Barriers and Facilitators

Tamará Oser, Sean M. Oser, Kanchi Bangalore Krishna, Daniel E. Hale, Hershey, PA

Children with both T1D and autism pose a distinct challenge, and there is exceedingly little research on T1D self-management in this special population and few resources to guide healthcare providers (HCPs) on how to best partner with families. This qualitative study used an exploratory inductive thematic approach to analyze a public internet forum authored by caregivers to children with both T1D and autism. All 398 posts were imported into NVivo 11 (QSR International). After codebook development, 3 researchers coded 10% and then 20% of the dataset, with Cohen’s kappa .994 and .998, respectively. With high inter-rater reliability established, coding of all remaining posts was then completed. Inductive thematic analysis revealed the following themes: 1.) Parents of children with T1D and autism yearned for support and did not feel understood by the autism community or the T1D community; social media provided much-needed peer support from families that understood the unique experience of raising a child with both conditions. 2.) Numerous coping techniques were discussed, including focusing on T1D management first, as glucose levels could affect behavior; establishing trust with teams with endocrinologists and autism specialists jointly developing treatments. 2.) Numerous coping techniques were discussed, including focusing on T1D management first, as glucose levels could affect behavior; establishing trust with teams with endocrinologists and autism specialists jointly developing treatments. 3.) Enhanced usual care (n=30). Over time, a significant increase in A1C (p<.03) was observed across groups overall, but not within study groups. After adjusting for multiple factors, younger age (p<.04, p<.004) and lower levels of DD (p<.04) were associated with improvements in A1C over time, while insulin use (p<.032) was associated with increases in A1C. A marked improvement in DD was observed (p<.04) overall. PL only (p<.003), PN+PL (p<.01), and A1C (p=0.02) were significantly associated with improvements in DD. Results suggest DD is a significant indicator of improvement in A1C levels. DD levels also improved following a faith community-based DSME intervention and were sustained by using the PL and PN DSMS infrastructure of the church. Opportunities to expand the DSMS infrastructure beyond churches and into other community organizations is needed.

Supported By: Bristol-Myers Squibb Foundation

874-P Clinical Practice Factors That Define Insulin Pump Readiness

Cassidy Puckett, Jennifer C. Wong, Ann Arbor, MI, Atlanta, GA, San Francisco, CA

The American Association of Clinical Endocrinologists/American College of Endocrinology and Endocrine Society guidelines on insulin pump use emphasize patient assessment to determine pump readiness for patients with type 1 diabetes (T1D). While guidelines mention the importance of the clinical practice context, such as the presence of a comprehensive pump management program and prescribing provider expertise in pump therapy, the primary emphasis is placed on the measurement of patient knowledge of diabetes management, their mental and psychological status, and adherence to self-care. But how clinics define and assess “pump readiness” is not standardized, and the extent to which this process is linked to systematic differences in the allocation of mechanical technologies by race and class is unclear. In this comparative qualitative study, we describe how two ADA recognized pediatric endocrinology centers with different prevalences of patient pump use (32% vs. 77% of patients with T1D) also differ in how they determine pump readiness. In the clinic with higher overall pump use, there are no differences in frequency of pump use between non-Hispanic white and ethnic minority patients, and differences by insurance status are small. In contrast, in the clinic with lower overall pump use, there are large differences in pump use by race and insurance status. To explore these trends, we conducted over 400 hours of observations of clinical encounters and decision-making processes and fifteen 30-minute interviews with pediatric endocrinologists, nurses, certified diabetes educators, and other staff and coded the data using Atlas.ti. Findings suggest pump allocation is shaped by how: 1) providers respond to patient “cultural capital” or interaction styles, 2) clinics frame and engage with medical technologies (e.g., “pump” practices as ongoing provider and patient education to support new devices), and 3) clinics organize provider care and decision making processes (e.g., professional opinion vs. use of metrics).
Behavioral Medicine, Clinical Nutrition, Education, and Exercise

POSTERS

875-P
Empowerment, Motivation, and Medical Adherence (EMMA)—Results of an RCT in Patients with Poorly Regulated Type 2 Diabetes

INNEMARIE R. VARMING, KASPER OLESEN, INGRID WILLAING, Gentofte, Denmark

Background: Many studies have shown that substantial improvement of glycemic control is difficult in patients with poor glycemic control. Knowledge, competences and motivation are critical requirements for optimal self-management and good glycemic control. The aim of this RCT was to test if a consultation program, EMMA could improve self-management and glycemic control in patients with T2D and poor glycemic control compared to a control group receiving usual care.

Methods: The study was a non-blinded parallel RCT targeting adults with T2D ≥ 1 year and HbA1c ≥ 64 mmol/mol in a Danish diabetes clinic. The intervention consisted of four consultations with nurses using EMMA, which provides a person-centered approach using dialogue tools designed to promote self-reflection, learning and goal-setting (3.5 months). Outcome measures were HbA1c and questionnaire scores investigating determinants of glycemic control according to Self-Determination Theory, such as autonomy support (Health Care Climate Questionnaire (HCCQ)). Consultation processes were evaluated by the level of nurse talk and the actual use of the tools.

Results: Eighty-seven participants completed the study (49 in the intervention group). The HCCQ score was significantly higher in the intervention group at end of the intervention. The increase in HCCQ score was not sustained at the end of follow-up (6 months). HbA1c was slightly reduced in both groups at the end of intervention and at follow-up. Average level of nurse talk in all recorded intervention consultations (n=57) was 37% of total talk-time. Records from the consultations showed that most of the reflection and goal-setting tools were used with >90% of the participants, whereas the learning tools were used with 61%.

Conclusion: The initial increase in autonomy support seemed attributed to the intervention. The non-significant decrease in HbA1c may be ascribed a short intervention period and less professional use of learning tools than intended.

876-P
Improved Diabetes Medication ConvenienCe in Persons with Type 2 Diabetes after Switching to Insulin Glargine 300 U/mL (U-300)—The Observational OPTIN-D Study

THIASR H. WIERINGA, MAARTJE DE WIT, JOS TWISK, FRANK J. SNOEK, Amsterdam, Netherlands

Insulin glargine-300 (U-300) provides a flatter and more prolonged profile than U-100, with less risk of hypoglycemia. Real-world evidence of the effect of U-300 on Patient Reported Outcomes (PROs) is lacking. Adults with type 2 diabetes (T2DM) using insulin for ≥6 months and initiating U-300 were included. Data were collected at baseline (start U-300; T0), 3 (T1) and 6 (T2) months (T2). Intention-to-treat mixed model analyses examined change over time in HbA1c, self-reported hypoglycemia and PROs: emotional well-being (WHO-5), hypoglycemia worries (HFS-W), diabetes distress (PAS-D), diabetes medication convenience (DSMRQ), sleep quality and duration (PSQI), and adherence (1-item SDSCA). Also, the extent to which U-300 fulfilled its expectations was measured at T2 both in physicians and patients. P-value threshold was set at 0.05 for the WHO-5 and .01 for other outcomes. In total, 162 persons with T2DM participated: 53.7% men, mean age 64.54 years (9.05). Baseline mean HbA1c 62.48 mmol/mol (12.61). Hypoglycemia incidence decreased non-significantly for symptomatic events from 31.5% (T0) to 24.8% (T2), nocturnal events from 6.8% (T0) to 4.1% (T2), severe events from 4.9% (T0) to 0.0% (T2). HbA1c trended towards a decrease to 60.32 mmol/mol (T2). Mean WHO-5 scores trended towards improvement, from 61.73 (T0) to 63.93 (T2). Mean DSMRQ scores improved significantly from 32.70 (T0) to 35.08 (T1) to 36.90 (T2) (β=0.02; p=0.001). Insomnia severity decreased non-significantly for symptomatic events from 9.05 (T0) to 8.39 (T1) to 8.44 (T2) (β=-0.02; p=0.001). Quality of life improved significantly for self-care factors and diabetes knowledge.

Conclusion: The initial increase in autonomy support seemed attributed to the intervention. The non-significant decrease in HbA1c may be ascribed a short intervention period and less professional use of learning tools than intended.

877-P
Gender Differences in Contributions of Mutable and Immutable Factors on Quality of Life in Adults with Type 2 Diabetes

JONI S. WILLIAMS, LEONARD E. EGEDE, Milwaukee, WI

Background: The aim of this study was to assess contributions of mutable and immutable factors on quality of life (QoL) in men and women with type 2 diabetes.

Methods: Cross-sectional study of 815 adults from two clinics in the southeastern U.S. Hierarchical models were performed for the full sample, and men and women using the physical component score (PCS) and mental component score (MCS) of QoL as dependent variables, adjusting for sociodemographic, socioeconomic, psychosocial, built environment, clinical, and self-care factors and diabetes knowledge.

Results: For women, significant associations were found between PCS QoL and neighborhood aesthetics (β=0.08; p=0.009) and exercise environment (β=0.03; p=0.010), accounting for 25% of the variance and MCS QoL, and various psychological distress (SPD) (β=0.12; p=0.001), perceived health status, (β=0.54; p=0.040) and diabetes knowledge (β=0.11; p=0.046), accounting for 36% of the variance. For men, significant associations were seen between PCS QoL and SPD (β=0.02; p=0.031), neighborhood crime (β=0.17; p=0.012), and kidney problems (β=0.25; p=0.045), accounting for 12% of the variance and MCS QoL and depression (β=0.08; p=0.004). SPD (β=0.07; p=0.002), perceived stress (β=0.14; p=0.001) diabetes duration (β=0.03; p=0.015), comorbidity (β=0.15; p=0.014), and perceived health status (β=0.28; p=0.045), accounting for 51% of the variance.

Conclusions: Significant associations were observed between QoL and mutable factors, suggesting areas amenable to health interventions. For women, interventions should focus on improving the built environment, decreasing SPD, and improving diabetes knowledge. For men, interventions should focus on the built environment, mental health, and comorbid conditions.

Supported by: National Institutes of Health (K24DK092899-01)
fied an effective PA intervention for adults with T2D that was nearly pragmatic enough for use in primary care. However, it still required adaptation to fit clinic work flows and to be reimbursed by insurance. After adapting the intervention (Be ACTIVE) to address these issues, we hypothesized Be ACTIVE would improve PA and physical function relative to randomized controls. This pragmatic pilot trial randomized adults with T2D to 12 weeks of Be ACTIVE (i.e. telephone behavioral counseling sessions + PA tracking (Fit-Bit®), 3 primary care visits to teach strength exercises + monitor safety) vs. enhanced usual care (3 self-management mailings). At baseline and post-intervention, we assessed PA with Actigraph® accelerometers (steps/week) and physical function by a timed 400-meter walk (sec) and the Short Physical Performance Battery (SPPB, 0-12 scale). To date, we have completed assessments for 15 participants (n=8 Be ACTIVE, n=7 controls). Pre-post PA increased by 19.8% in the Be ACTIVE group (+5122 ± 1008 steps/week; t(16) = 5.20, p<0.001) and physical function by a timed 400-meter walk improved by 10.3% in Be ACTIVE participants (-3.3 ± 6.6 sec) and declined by 5.4% in controls (+1.3 ± 6.4 sec). Be ACTIVE is a reimbursable intervention delivered by primary care staff. Strong pilot data support that Be ACTIVE improves PA/physical function. If Be ACTIVE is a reimbursable intervention delivered by primary care staff, this could allow expanded access to depression treatment for T2DM patients in rural and urban areas.

**Predictors of Depressive Symptoms in a Clinical Sample of Individuals with Type 1 Diabetes**

**KELLY R. STANEK, SHIDEH MAJIDI, JO M. VOGELLI, KIMBERLY A. DRISCOLL, Aurora, CO**

Background: Depression screening during routine type 1 diabetes (T1D) clinical care is increasing, but no studies have examined predictors of symptoms in a clinical sample of those with T1D.

Methods: Individuals with T1D ages 18-25 years completed the Patient Health Questionnaire-9 (PHQ-9) during routine T1D clinic visits. PHQ-9 scores range from 0-27 with higher scores reflecting more depressive symptoms. Demographic and T1D-specific characteristics were also collected.

Results: A total of 609 individuals with T1D were screened: 43% female; mean 15.2±3.1 years; 76% Caucasian; 11% Hispanic; 70% private insurance; mean A1C = 8.9±2.2%; mean T1D duration = 5.9±4.4 years; 49% insulin pump (CSII); 26% continuous glucose monitor (CGM). Average PHQ-9 score was 4.0±4.6 (range = 0-24; 67% minimal, 22% mild, 7% moderate, 3% moderately severe, 1% severe). Linear regression analyses revealed female sex, having public insurance and higher A1Cs, and lack of CGM use were significantly associated with higher depressive symptoms (Table). Older age and lack of CSII trended towards significance.

Conclusions: The results of this study demonstrate the importance of screening for depressive symptoms as part of routine T1D clinical care. Results further support potentially targeting individuals with specific characteristics (e.g., 3-4 times, high A1C) for screening when clinic resources to implement screening are limited.

**Table. Predictors of Depressive Symptoms.**

<table>
<thead>
<tr>
<th></th>
<th>β</th>
<th>SE</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.066</td>
<td>0.059</td>
<td>0.096</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.004</td>
<td>0.363</td>
<td>0.936*</td>
</tr>
<tr>
<td>Insurance</td>
<td>-0.100</td>
<td>0.304</td>
<td>0.031*</td>
</tr>
<tr>
<td>A1C</td>
<td>0.150</td>
<td>0.083</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>Pump Use</td>
<td>-0.074</td>
<td>0.305</td>
<td>0.085</td>
</tr>
<tr>
<td>CGM Use</td>
<td>-0.099</td>
<td>0.251</td>
<td>0.021*</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01, ***p<0.001.

Supported By: National Institutes of Health

**Clinic-Wide Screening of Fear of Hypoglycemia in Mothers and Fathers of Children with Type 1 Diabetes**

**SHIDEH MAJIDI, HOLLY O’DONNELL, KYLEE BENSON, KIMBERLY A. DRISCOLL, Aurora, CO**

Background: The American Diabetes Association (ADA) recommends anxiety screening in individuals with type 1 diabetes (T1D); however, screening in parents is not addressed. This study describes fear of hypoglycemia (FOH) in parents who were screened as part of their children’s routine T1D clinic visit.

**Table. Predictors of Depressive Symptoms.**

<table>
<thead>
<tr>
<th></th>
<th>β</th>
<th>SE</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.066</td>
<td>0.059</td>
<td>0.096</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.004</td>
<td>0.363</td>
<td>0.936*</td>
</tr>
<tr>
<td>Insurance</td>
<td>-0.100</td>
<td>0.304</td>
<td>0.031*</td>
</tr>
<tr>
<td>A1C</td>
<td>0.150</td>
<td>0.083</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>Pump Use</td>
<td>-0.074</td>
<td>0.305</td>
<td>0.085</td>
</tr>
<tr>
<td>CGM Use</td>
<td>-0.099</td>
<td>0.251</td>
<td>0.021*</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01, ***p<0.001.

Supported By: National Institutes of Health

**A229**
Methods: Mothers (n=234) and fathers (n=79) completed the Hypoglycemia Fear Survey - Parent comprising 3 subscales: Maintaining High Blood Glucose (BG), Worry/Helplessness About Low BG, and Worry About Negative Social Consequences. Scores of ≥7, ≥4, and ≥8, respectively, were used as clinical cut-offs. Higher scores indicate greater fear/worry about hypoglycemia.

Results: Child characteristics were: 53% female, mean age = 13.9±2.2 years; mean A1C = 9.3±2.2%, mean T1D duration = 5.1±4.1 years; 58% CII. Percentage of mothers and fathers exceeding the clinical cut-offs were: 18%, 14% on Maintaining High BG, 15%, 3% Worry/Helplessness About Low BGs; and 14%, 1% Worry About Negative Social Consequences. Compared to fathers, mothers reported significantly more helplessness about low BGs (t(173.6)=3.24, p<0.001), but not more worry about negative social consequences (t(223.4)=1.42, p=0.16), or engaging in behaviors to maintain high BGs (t(290)=0.68, p=0.50). Parents of older children (≥13 years) worried equally about hypoglycemia (p=0.05), but reported engaging in fewer behaviors to maintain high BGs than parents of younger children (10-12 years) (t(307)=3.27, p<0.001).

Conclusions: FOH is common in both mothers and fathers. Mothers reported more feelings of helplessness than fathers, whereas both mothers and fathers of younger children reported engaging in more behaviors to maintain high BGs than parents of older children. These results support the need to screen parents, not just patients with T1D, for FOH and provide intervention when indicated. Consideration should be given to including recommendations about FOH screening parents in the ADA Medical Standards of Care.

Supported By: National Institutes of Health (103DK110459)

884-P

A Real-World Evidence in Understanding the Barriers and Behaviours of Insulin Therapy among Indian Type 2 Diabetes Mellitus (T2DM) Patients

PRAVEEN RAJ, DILIP PAWAR, SARAH JABEEN, SHIVARAM VS, KABALGA, India

Introduction: American Diabetes Association categorizes barriers to adherence as either patient barriers, medication factors, or system factors. The aim of the study is to understand the barriers and behaviors of insulin therapy among T2DM patients in India from a real world setting.

Methods: The data is collected from an ongoing patient support program called as iTAP (Insulin Therapy Assistance Program) designed by Biocon in patients with T2DM receiving insulin. It is an open label, multicentric, real world data depicting 10426 T2DM patients, of which 3192 (30.61%) patients have moved on to various therapies observed over 9 months. Data of these 3192 patients were analyzed to understand the reasons for shift in therapy.

Results: The prime behavioral change is from insulin to oral hypoglycaemic drugs (64.35%) and others are, short term insulin therapy (12.81%), and change/shift from an ampoule to vial dosage (6.11%). The primary barriers in insulin therapies were hypoglycaemic episodes (25.9%), stress (17.1%), fear of injection (10.3%) and cost (7.4%).

Conclusion: There is an overwhelming amount of data on interventions to address those barriers or even aimed at improving insulin adherence in general. Education and empowerment (stress, fear of injection and cost) through shared decision-making allow patients’ preferences to be presented and subsequently generate the best individualized treatment plan for each patient.

Supported By: Bristol-Myers Squibb Foundation

885-P

An Examination of the Presence of Mental Health Diagnoses in a Clinical Sample of Individuals with Type 1 Diabetes

KELLY R. STANEK, SHIDEH MAJIDI, ERIN M. YOUNGKIN, JO M. VOGELI, KIMBERLY A. DRISCOLL, Aurora, CO

Objective: To examine demographic and mental health diagnostic characteristics for individuals with type 1 diabetes (TID) and current mental health diagnoses.

Methods: The medical records of 397 individuals ages 10-25 with TID (mean age = 15.3±3.1 years, mean T1D duration = 6.0±4.5 years) who were screened during routine T1D clinic visits for depressive symptoms using the Patient Health Questionnaire-9 (PHQ-9) were reviewed for current DSM-5 diagnoses, demographic information, and T1D management data.

Results: Of those screened, 29% had a mental health diagnosis; 56% had 1 diagnosis, 26% had 2, and 18% had 3+. The most common diagnoses were depression (16% of total screened), anxiety (15%), and attention-deficit/hyperactivity disorder (10%). Other diagnoses included mood, learning, and eating disorders. Those with a mental health diagnosis were slightly older and they had higher PHQ-9 scores and higher HbA1c (Table). Sex, race, insulin regimen, continuous glucose monitor use, T1D duration, and insurance were not significantly different.

Conclusions: Mental health diagnoses are common in adolescents and young adults with T1D. Those with mental health conditions may experience greater difficulties in T1D management, contributing to higher HbA1c. There is a need to develop tailored interventions to improve T1D management when specific mental health conditions are present.

Table. Differences in Characteristics between T1D Youth With and Without a Mental Health Diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Mental Health Diagnosis</th>
<th>No Mental Health Diagnosis</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>15±8±2.9</td>
<td>15±0±2.2</td>
<td>0.023</td>
</tr>
<tr>
<td>PHQ-9 Score</td>
<td>7.5±8.4</td>
<td>3.8±4.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>A1C</td>
<td>9.8±8.25</td>
<td>9.1±7.2</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Supported By: National Institutes of Health

886-P

RCT of Tailored Cognitive Behavioral Intervention Reduces Regimen-Related Distress—Relationship to Change in Medication Adherence and Glycemic Control at 12-Month Follow-Up

LESLEY LUTES, DOYLE M. DUMMING, BERTHA HAMIDSHGE, MARISSA CAR-RAWAY, SHIVAJIRAO PATIL, ALYSSA ADAMS, CHELSEY SOLAR, KERRY LITTLEWOOD, SHEILA EDWARDS, PEGGY GALVIN, Kelowna, BC, Canada, Greenville, NC, Tampa, FL

Elevated regimen related distress (RRD) in type 2 diabetes (T2D) is associated with poor glycemic control and lower medication adherence but the strategy for and impact of reducing RRD in primary care is unclear. Data for this study comes from a prospective randomized controlled trial that evaluated the effectiveness of a 16-session tailored cognitive behavioral intervention plus lifestyle change counseling (n = 67, IG-intervention group) delivered by trained staff compared to usual care (n = 72, CG-control group) in 139 adult rural patients (mean age = 52 ± 9.5 years; 72% black; BMI = 37.0 ± 9.0) with uncontrolled (mean A1C = 9.6 ± 2.0) T2D (52% on insulin) and co-morbid depressive (PHQ-2) or distress (DDS-2) symptoms at screening in an academic primary care clinic. At baseline and at 12-month follow-up: A1c, regimen-related distress (sub-score of DDS-17), depressive symptoms (PHQ-9), self-care behaviors (SDSCA), and medication adherence (ModMAS) were measured using validated instruments. There were no differences between groups at baseline in mean age, race, gender, or mean values for A1c, body mass index (BMI), PHQ-9, or RRD scores. At 12-month follow-up patients in the behavioral intervention group had significantly greater reduction in RRD scores than those in the control arm (t(1.12) = 1.05 vs. -0.31 ± 1.22; p = 0.001). Among intervention group patients only, those with an improvement in RRD score of ≥1 (n = 32) had substantially greater improvement in A1c (-1.3 ± 1.7 vs. -0.56 ± 1.3; p = 0.09) and self-care behaviors (+1.33 ± 1.38 vs. +0.88 ± 1.2; p = 0.16) as well as significantly greater improvement in medication adherence (+1.6 ± 1.7 vs. +0.47 ± 2.2; p = 0.02). A tailored cognitive behavioral intervention reduces RRD in patients with uncontrolled T2D and co-morbid behavioral problems and is associated with improved medication adherence that may be associated with improved glycemic control.

Supported By: Bristol-Myers Squibb Foundation

887-P

Determination of Risk for Suboptimal Glycemic Control in New-Onset Type 1 Diabetes

SHIDEH MAJIDI, JO M. VOGELI, KIMBERLY A. DRISCOLL, Aurora, CO

Background. Most youth with type 1 diabetes (T1D) do not meet current ADA recommendations for A1c, thus, it is important to identify at diagnosis, those at-risk for later suboptimal glycemic control (A1c ≥ 9.5%) and complications.

Methods: The Risk Index for Poor Glycemic Control (RI-PGC) was administered to 266 parents during children’s (ages <1-19 years) routine new onset T1D visit. The RI-PGC provides a single score (range = 0-9, higher scores = higher risk) based on psychosocial factors (e.g., insurance, child mood, parent stress/anxiety) to classify risk as “Low,” “Moderate,” or “High” in the 1-4 years after diagnosis. Demographic data and DKA occurrence at diagnosis were also collected.

Results: Of 266 children with new onset T1D (Mage 9.98 ± 4.42 years; 52% male, 68% caucasian), 18.8% and 28.6% were Moderate and High Risk, respectively. DKA at onset (n=17, 59%) was significantly correlated with risk score (r=0.88, p<0.001). Children in DKA at onset were more than twice as likely to score high on RI-PGC (p=0.009; Table).

Supported By: National Institutes of Health
Conclusions: We use the RI-PGC in a prevention program to identify risk of future suboptimal glycemic control. These results are consistent with the only other study (Schwartz et al., 2014) to examine risk-most children were Low Risk and more children were High Risk than Moderate Risk. Presence of DKA at onset may be another predictor of future suboptimal glycemic control, DKA episodes, and complications.

**Table. Risk Classification at T1D New Onset for Later Complications.**

<table>
<thead>
<tr>
<th>RI-PGC Risk Category (%)</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>DKA at Onset</td>
<td>75 (54%)</td>
<td>26 (52%)</td>
<td>56 (74%)</td>
</tr>
<tr>
<td>No DKA at Onset</td>
<td>65 (46%)</td>
<td>24 (48%)</td>
<td>20 (26%)</td>
</tr>
</tbody>
</table>

Supported By: National Institutes of Health (SK2DK094712-07)

**Preferences for Health Information and Decision-Making Autonomy among Chinese Patients with T2DM in the mHealth Era**

LISA NIE, BO XIE, YAN YANG, SHARON A. BROWN, Austin, TX; Chengdu, China

This cross-sectional survey explored (1) individual preferences for health information and decision-making autonomy among Chinese patients with type 2 diabetes (T2DM); (2) their use of mHealth in diabetes self-management; and (3) the relationship between their mHealth use and preferences for health information and decision-making autonomy. Sample size: 200 Mandarin-speaking Chinese patients with T2DM; age range: 26-80 years (Mean: 59.91, SD: 12.17); Mean time since diabetes diagnosis: 7.4 years. Data were collected in February 2017 via a paper-and-pen questionnaire at a general hospital in China. The questionnaire was in Chinese, and measured preferences for health information and decision-making autonomy and mHealth use. Key findings: Participants wanted a wide range of health information and participation in decision-making. Gender, health status, and knowledge about diabetes were associated with differences in information wanted and participation in decision-making, but age was not. Half (50.5%) of the participants used smartphones to access the internet and look for health information; 71% used smartphones to receive/read health-related posts; and 24% had at least one health-related application installed on their smartphones. Smartphone use frequency for health information and participation in decision-making had a significant interaction effect (p < .05), the strength of which varied across seven subscales (specific health condition, treatment, laboratory tests, self-management, complementary/alternative medicine, psychosocial aspects, and healthcare providers). The overall health information wanted was positively related to use of smartphones to receive health-related posts (p < .05). This study has implications for research and clinical practice, especially given the shift from smartphones to connected patient-centered care and increasing use of mobile technology in health care.

**Reasons for Insulin Omission—What Matters Most?**

CHANDRA Y. OSBORN, LINDSAY E. SEARS, ASHLEY HIRSCH, JENNIFER RAYMOND, MARK HEYMAN, RACHEL HEAD, CHANDRA Y. OSBORN, Nashville, TN; New York, NY; Los Angeles, CA

Background: One in 3 people with diabetes (88% with type 2 diabetes [T2D]) do not take insulin as recommended an average ~3.3 days per month. Insulin omission (IO) is associated with suboptimal A1c. Reasons for IO are multifactorial (e.g., cost, fear, stigma). Unclear are what matters most for reducing IO and improving A1c.

Objective: We assessed 10 reasons for IO among a national sample of people with T2D, and identified reasons that, if addressed, might improve A1c.

Methods: Adults (age 18-75 years) with T2D self-selected to be in a randomized control trial comparing inhalable, ultra-rapid-acting insulin (Afrezza) with One Drop vs. injectable, rapid-acting insulin with One Drop. Eligible persons completed an online survey and NGSP certified A1c test. Survey items collected demographic information and responses to the Adherence to Refills and Medications Scale for Diabetes (ARMS-D) administered for insulin only. SPSS and PROCESS v3.0 were used for descriptive statistics and unadjusted and adjusted mediation models with bootstrapped (10K) CIs for tests of indirect effects.

Results: Participants (N=269) were 50±11 years old, 51% male, 30% non-white, with 13±8 years since a T2D diagnosis, and A1c 8.8% ± 1.8%. Compared to NHWs, non-whites were less adherent to their insulin regimens (ARMS-D = 35.4 ± 37.2, p < .05) and had a higher A1c (9.2% vs. 8.8%, p < .05). Among younger adults (<49.94 years old), not taking enough insulin was a mechanism linking non-white race/ethnicity to having a higher A1c (unadj. coef.=.40, 95% CI: .09, .79; adj. coef.=.33, 95% CI: .01, .77). Among people over age 50, there was no indirect effect of non-white race/ethnicity on higher A1c via less adherence to insulin.

Discussion: Reducing disparities in insulin adherence may reduce disparities in A1c for younger adults, but not older adults. Other mechanisms underlying diabetes disparities may be age- or cohort-specific. Understanding these nuances can inform interventions aimed at reducing disparities in diabetes.

**Assessment of Diabetes Distress in Appalachian Ohio**

ELIZABETH A. BEVERLY, EMILY H. GUSEMAN, KARIE A. COOK, AMBER M. HEALY, Athens, OH

Diabetes rates in southeastern Ohio are more than double the national average (19.9% vs. 9.4%). Here, people battle a poverty rate 1.5 times that of the U.S. average, and suffer from higher unemployment, lower educational achievement, poorer health, and lower access to care. Despite the high presence of social determinants of health, the impact of diabetes is understudied and one critical outcome that has not been addressed is diabetes distress. We conducted a cross-sectional survey study with 121 students, faculty, and staff at a large university in Appalachian Ohio (A1C=7.3±1.4%, age=36±17years; female=60%; white=86%; type 2 diabetes=54%; duration=10±9 years, 48%=college degree or more). Diabetes distress was assessed using the Diabetes Distress Scale for type 2 diabetes and for type 1 diabetes; depressive symptoms were assessed using the Patient Health Questionnaire-9. Of the 65 type 2 diabetes participants, 34% (n=19) reported moderate to severe diabetes distress, with 48% (n=31) experiencing moderate to severe distress on the Regimen subscale. Among the 56 type 1 participants, 26% (n=15) reported moderate to severe diabetes distress, with 51% (n=28) experiencing moderate to severe distress on the Powerlessness subscale. Multiple regression analyses found high scores of diabetes distress (standardized b=0.62, p=0.03) were independently associated with higher A1c levels after controlling for depressive symptoms (standardized b=0.01, p<.01), age (standardized b=-0.03, p=0.14) and gender (standardized b=0.75, p<.08). This model accounted for 29% of the variation in A1C. Multiple regression analyses using the same model found no association between type 2 diabetes, distress, and A1C, the lack of discrimination...
of significance may be explained by well-educated, working adults with private insurance. Next steps include recruiting type 1 and type 2 patients from local specialty and primary care clinics to enhance representativeness. These data will help providers individualize clinical approaches for patient’s diabetes distress level.

Supported By: American Osteopathic Association

892-P

Shared Telemedicine Appointments for Young Adults with T1D and Depressive Symptoms—Improved Attendance and Symptom Regulation

MARK W. REID, JENNIFER RAYMOND, JOHN F. THOMAS IV, Los Angeles, CA; Aurora, CO

Background: Adherence to care recommendations for type 1 diabetes (T1D) may be complicated by the presence of depressive symptoms. Shared medical appointments (SMA) for T1D via home telemedicine may uniquely address the needs of depressed young adult T1D patients (YA), since the treatment model encourages social interaction and support while patients are safe at home.

Objective: Evaluate the efficacy of SMA via home telemedicine for improving care adherence and depressive symptom regulation in YA with T1D.

Methods: Participants in the Colorado Young Adults with T1D (CoYoT1) prospective study of SMA via home telemedicine completed the Center for Epidemiologic Studies Depression scale (CES-D) at baseline and after one year. We calculated somatic and cognitive CES-D subscale scores based on its theorized factor structure.

Results: Patients in CoYoT1 did not experience significant changes in depressive symptoms, but males in the control group, who only attended in-person appointments, reported significantly higher depressive symptoms after one year (see Figure 1, p = 0.03). Further, among those with depressive symptoms at baseline, CoYoT1 patients attended one more appointment on average than control patients (1.9 vs. 0.9, p = 0.008).

Conclusions: SMA via home telemedicine may help YA with T1D regulate depressive symptoms, while also promoting clinic attendance.

Figure 1. Changes in Depressive Symptoms over Time by Sex and Study Group (CoYoT1 versus Control)

Supported By: The Leona M. and Harry B. Helmsley Charitable Trust

893-P

Experiences of Enrolling in the U.S. Monogenic Diabetes Registry

SALLY S. LADSARIA, JAZZMYNE MONTGOMERY, KATHERINE L. LINDAUER, ROCHELLE N. NAYLOR, Chicago, IL

The U.S. Monogenic Diabetes Registry (Registry) facilitates accurate genetic diagnosis, gene-directed management and longitudinal follow-up of monogenic diabetes. Through the Registry, we currently follow 569 individuals with MODY, 74% of who have had genetic testing through Registry-related studies. We aimed to understand participants’ experiences of accessing, enrolling and participating in the Registry.

Through one-on-one semi-structured interviews participants were queried on how they were diagnosed with MODY, understanding of their diagnosis, and their experiences as Registry participants. An iterative process of coding, analyzing, and summarizing transcripts was completed using thematic analysis.

Data collection and analysis are ongoing. To date, we have conducted 8 interviews. Prolonged misclassification of diabetes type and delayed consideration of and referral for monogenic diabetes evaluation were commonly reported. Participants reported negative effects from diabetes misclassification, including emotional, financial and treatment burden. Participants were generally positive regarding interactions with the Registry. However, long turnaround times for research-based genetic testing results negatively impacted some participants. Levels of provider knowledge, healthcare access, socioeconomic status (SES), culture, language and self-efficacy were identified as important facilitators or barriers to Registry referral and enrollment for accurate MODY diagnosis.

Our study demonstrates multiple negative impacts of delay in MODY diagnosis. It also shows the utility of the Registry in aiding in MODY diagnosis. Efforts should focus on increased visibility of the Registry to diabetes providers and directly to patients. Specific measures to increase knowledge of and facilitate enrollment in the U.S. Monogenic Diabetes Registry among lower SES patients, non-native English speakers and racial and ethnic minorities can help address apparent ascertainment bias within the Registry.

Supported By: National Institutes of Health (K23DK114564)

894-P

Long-Term Use of Closed-Loop Control—Patient-Reported Experience

LINDA GÖNDER-FREDERICK, SUE A. BROWN, JACLYN SHEPARD, LAURA L. KOLLAR, BORIS KONATCHEV, Charlottesville, VA; Jeffersonon, VA

Objective: Assess patient experience via semi-structured interviews after long-term outpatient use of closed loop control (CLC).

Methods: Eleven patients with T1D diagnosed for at least one year participated (10 females), with a mean (SD) age of 47.3 years (12.9), diabetes duration of 28.6 years (17.7), and pre-study HbA1c 7.6% (0.5%) or 60 mmol/mol. The CLC system was inControl, composed of a CGM, insulin pump, and control algorithms housed on a smartphone. Participants used inControl for 8-weeks after which they were interviewed. Interviews followed a semi-structured format based on theories of technology acceptance. Numerical ratings were obtained for difficulty, complexity, trust, and long-term use probability on a 5-point Likert scale.

Results: Ratings were: difficulty - 2.0 (0.8), complexity - 1.9 (0.8), trust - 3.8 (1.0), and 41% probability of long-term use - 3.3 (1.8). Difficult aspects of use were managing the three components and alarms for out of range BGs. The major complexities were finding ways to stop alarms and understanding insulin bolus calculation. Nine patients reported that the device was very useful and had improved BG control, including decreasing low BGs and reducing HbA1c. All reported “over-riding” the device, most often to give more insulin for high BG correction, and also detaching the system at times to avoid alarms. Trust in the device was high, with 8 patients rating ≥ 4 but there was belief that not enough insulin was given for high BGs. Probability of long-term use varied, with the alarms and burden of multiple components as factors.

Conclusions: Patient-reported experiences varied across individuals. The majority did not find the system difficult or complex, found it useful for better BG control, and trusted it. However, there is need for technology improvement to reduce equipment burden and alarms. Findings indicate that users might benefit from patient education before device use to help them understand how the system calculates insulin doses.

Supported By: National Institutes of Health (R01DK085623)

895-P

Quality of Life Assessment in Patients with HNF1A- and GCK-MODY Compared with T1DM

MAGDALENA SZOPA, Krakow, Poland

Maturity onset diabetes of the young (MODY) constitutes a few percent of this disease, with HNF1A- and GCK-MODY being its most common forms. We examined the impact on QoL (Quality of Life) of monogenic diabetes among patients with HNF1A-MODY or GCK mutation carrier status and compared it to type 1 diabetic (T1DM) individuals.

Methods: The study included 80 patients with HNF1A-MODY and 89 GCK gene mutation carriers (45 patients with diabetes and 44 prediabetic). We also examined 128 T1DM patients as a control group. Diabetes-specific QoL was assessed using the Audit of Diabetes Dependent Quality of Life questionnaire.

Results: Both HNF1A-MODY and GCK-MODY groups had similar mean age (41.7 vs. 38.0 years, respectively) and BMI (24.1 vs. 24.3 kg/m²), whereas T1DM patients were younger (34.2 years) with similar BMI (25.0 kg/m²). Less than a third of GCK mutation carriers were on pharmacotherapy (31%), while the majority of HNF1A mutation carriers used oral drugs or insulin (82.5%) (p=0.001). While QoL were similar in three groups (p=0.66), both the impact of diabetes on the patient’s QoL and the average weighted impact (AWI)
Hemoglobin A1C has:

Outcome
Comparison of College Students (18-25) Who Are Members and with other students with T1D may have health benefits. These findings organization. University-based diabetes student organizations and connect-

Member participation compared college students with T1D who are members of a uni-

College students with type 1 diabetes (T1D) face a number of stressors during their transition to college. While all students encounter a new environment, late nights, erratic schedules, sleep disruption, changed support

Since becoming a member and starting college my:

Table 1. Comparison of College Students (18-25) Who Are Members and Non-members of a University-Based Student Diabetes Organizations (n = 371).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Member N (%)</th>
<th>Non-Member N (%)</th>
<th>Test</th>
<th>Statistic</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of isolation has:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased significantly</td>
<td>80 (24.6%)</td>
<td>62 (26.4%)</td>
<td></td>
<td></td>
<td>0.017</td>
</tr>
<tr>
<td>Decreased</td>
<td></td>
<td>118 (48.8%)</td>
<td>24 (10.9%)</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Not changed/the same</td>
<td>54 (22.1%)</td>
<td>66 (29.0%)</td>
<td></td>
<td></td>
<td>0.22</td>
</tr>
<tr>
<td>Increased</td>
<td>104 (41.1%)</td>
<td>26 (10.5%)</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Number of low blood sugar events</td>
<td></td>
<td></td>
<td>Fisher’s Exact a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased significantly</td>
<td>31 (12.6%)</td>
<td>24 (10.9%)</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Decreased</td>
<td>26 (11.5%)</td>
<td>19 (10.5%)</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Not changed/the same</td>
<td>196 (81.2%)</td>
<td>50 (39.4%)</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Increased</td>
<td>13 (5.3%)</td>
<td>26 (20.5%)</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Increased significantly</td>
<td>20 (8.2%)</td>
<td>32 (26.4%)</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Hemoglobin A1C has:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowered</td>
<td>75 (33.2%)</td>
<td>43 (35.0%)</td>
<td></td>
<td></td>
<td>0.52</td>
</tr>
<tr>
<td>Not changed</td>
<td>132 (58.4%)</td>
<td>26 (21.1%)</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Risen</td>
<td>18 (8.4%)</td>
<td>50 (40.3%)</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Depression has:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased significantly</td>
<td>36 (14%)</td>
<td>11 (32.4%)</td>
<td></td>
<td></td>
<td>0.0001</td>
</tr>
<tr>
<td>Decreased</td>
<td>27 (10%)</td>
<td>9 (27.3%)</td>
<td></td>
<td></td>
<td>0.0001</td>
</tr>
<tr>
<td>Not changed</td>
<td>37 (14%)</td>
<td>11 (32.4%)</td>
<td></td>
<td></td>
<td>0.0001</td>
</tr>
<tr>
<td>Increased</td>
<td>45 (17.5%)</td>
<td>30 (95.3%)</td>
<td></td>
<td></td>
<td>0.0001</td>
</tr>
<tr>
<td>Anxiety has:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased significantly</td>
<td>25 (9.8%)</td>
<td>14 (43.3%)</td>
<td></td>
<td></td>
<td>0.0001</td>
</tr>
<tr>
<td>Decreased</td>
<td>17 (6.7%)</td>
<td>26 (82.3%)</td>
<td></td>
<td></td>
<td>0.0001</td>
</tr>
<tr>
<td>Not changed</td>
<td>61 (24.4%)</td>
<td>26 (82.3%)</td>
<td></td>
<td></td>
<td>0.0001</td>
</tr>
<tr>
<td>Increased</td>
<td>6 (2.4%)</td>
<td>26 (82.3%)</td>
<td></td>
<td></td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Conclusions: Diagnosis of the most frequent subtypes of MODY has a negative impact on QoL for affected individuals, although, it is smaller than in T1DM. Mode of treatment seems to influence QoL for HNF1A-MODY patients, both indices were larger in HNF1A-MODY patients than in GCK-MODY patients, but there was no significant difference in the impact of diabetes between these groups. In T1DM patients, all three major indices of QoL were more affected for patients on insulin as compared to the other individuals.

Supported By: Polish Diabetes Association

Cross-border diabetes is a major public health challenge that affects millions of people worldwide. According to the International Diabetes Federation, the number of people with diabetes is expected to rise from 422 million in 2015 to 629 million in 2040. Cross-border diabetes presents unique challenges to healthcare providers, who must navigate complex health systems and cross-border regulations. This study aimed to explore the experiences of patients with cross-border diabetes, and their perspectives on healthcare delivery across national borders.

Introduction: Cross-border diabetes is a growing challenge that affects millions of people globally. Diabetes patients often have to navigate the complexities of cross-border care, which can impact their quality of life and access to appropriate treatment. This study aimed to explore the experiences of patients with cross-border diabetes and their perspectives on healthcare delivery across national boundaries.

Results: A total of 52 participants were recruited from three countries: the USA, Canada, and Mexico. The majority of participants were from the USA (n=30), followed by Canada (n=12) and Mexico (n=10). The majority of participants were adults (86%), with a median age of 55 years (range: 21-75 years). The majority of participants were diagnosed with Type 1 diabetes (n=39), followed by Type 2 diabetes (n=10) and other types (n=3).

Discussion: Cross-border diabetes can significantly impact the quality of life for patients, who often face challenges related to accessing care, navigating healthcare systems, and managing their condition across national borders. Future research is needed to explore the best practices for delivering cross-border diabetes care and to develop policies that support patients with cross-border diabetes.

Supported By: National Institute of Diabetes and Digestive and Kidney Diseases

Frequency of Flash Glucose Monitoring Scans and Hemoglobin A1c in Real Life

ANDREA LAURENZI, AMELIA CARENTI, MARILUCE BARRASSO, ANDREA MARIO BOLLA, CHIARA MOLINARI, ANNA ZANARDINI, NICOLETTA C. DOZIO, ELENA MENENSHI, EMANUELE BOSI, MARINA SCAVINI, Milan, Italy; Centro Diabetologia Balsamo, Italy

Introduction: In patients with type 1 diabetes mellitus (T1D) the relationship between low number of self-monitoring of blood glucose (SMBG) measurements and elevated hemoglobin A1c (HbA1c) levels has been reported. However, the optimal frequency of SMBG has not been defined. Flash glucose monitoring (FGM) is an emerging technology allowing patient with diabetes to measure interstitial glucose concentrations in a non-invasive manner, with patients obtaining more measurements than with SMBG.

Materials and Methods: We collected data from 103 adult T1D patients using FGM technology in real life for at least 28 days. We recorded patients demographics, diabetes duration, type of treatment (CSII or MDI) and we downloaded FGM data to the Abbott Freestyle Libre software, which provides the number of daily FGM scans and estimates of HbA1c based on continuous glucose profile readings. The correlation between median FGM
Hemoglobin A1C has:

- χ^2 (df=2) = 38.8, p<.0001 for patients with diabetes mellitus (T1D) compared to non-diabetic controls.
- χ^2 (df=1) = 6.3, p<.0001 for patients with type 2 diabetes (T2D) compared to non-diabetic controls.

Outcome a: Non-Members of a University-Based Diabetes Student Organizations (n = 371).

Table 1.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Member N (%)</th>
<th>Non-Member N (%)</th>
<th>Test</th>
<th>Statistic</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Since becoming a member and starting college:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level of isolation has:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased significantly</td>
<td>60 (24.6%)</td>
<td>9 (20.9%)</td>
<td>Fisher's Exact</td>
<td>p&lt;.0001</td>
<td></td>
</tr>
<tr>
<td>Decreased</td>
<td>119 (48.9%)</td>
<td>24 (19.8%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not changed/the same</td>
<td>54 (22.1%)</td>
<td>66 (52.0%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>104 (41.1%)</td>
<td>26 (20.5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of low blood sugar events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher's Exact</td>
<td>p&lt;.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression has:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>15 (5.3%)</td>
<td>52 (41%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not changed</td>
<td>13 (5.3%)</td>
<td>52 (41%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety has:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>28 (11.5%)</td>
<td>19 (15.0%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not changed</td>
<td>28 (11.5%)</td>
<td>19 (15.0%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin A1C has:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowered</td>
<td>75 (33.2%)</td>
<td>43 (35.0%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not changed</td>
<td>120 (54.8%)</td>
<td>26 (21.1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risen</td>
<td>19 (8.4%)</td>
<td>54 (43.9%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression has:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>34 (14.8%)</td>
<td>11 (29.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not changed</td>
<td>37 (15.9%)</td>
<td>41 (33.8%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety has:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>29 (11.1%)</td>
<td>39 (31.0%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not changed</td>
<td>61 (26.4%)</td>
<td>71 (56.3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gotten better</td>
<td>87 (35.7%)</td>
<td>26 (20.5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*All outcome variables relate to when in college; a: Fisher's Exact; low cell counts; b: diabetes ketoacidosis.

Diabetes Prevention within a Large Health Care System

KISTEN M.J. AZAR, CATHERINE NASRALLAH, NINA SZWERINSKI, VIDITA CHOPRA, MEGHAN HALEY, ROBERT ROMANELLI, Walnut Creek, CA; Palo Alto, CA

Background: The Group Lifestyle Balance™ (GLB) program is an adaptation of the landmark Diabetes Prevention Program that has been recognized by the CDC as a model curriculum for diabetes prevention. The implementation of GLB at 8 predominantly autonomous and highly diverse clinics within a single, large multi-specialty healthcare organization provides a unique opportunity to evaluate the program in a real-world setting.

Methods: We conducted structured interviews with GLB facilitators at Sutter Health, a Healthcare Delivery System in Northern California, using snowball sampling. Interview questions were based on the RE-AIM framework to explore the reach, effectiveness, adoption, implementation and maintenance of the program between sites. We focused this analysis on a single regional affiliate of Sutter, with 8 clinic sites offering GLB to examine potential within-region variation.

Results: Ten GLB facilitators were interviewed, representing 8 clinical sites within the Sutter Health regional affiliate. All the facilitators were diabetes educators; 9 were registered dietitians and 1 was a registered nurse. Five sites began offering GLB in 2010, followed by two sites in 2013 and one in 2015. Eligibility criteria were the same across sites, and included all patients regardless of risk factors, except pregnant women. While all sites consistently offer 12 weekly “core” sessions over a 3-month period, the maintenance sessions are optional and are only offered at half of the sites. Almost all facilitators (n=9) reported that they use a modified version of the curriculum developed by the University of Pittsburgh and all mentioned that they provide participants with additional information.

Conclusion: These preliminary data suggest that the GLB program has been implemented within a regional affiliate of a healthcare system, consistently, yet with some variation in the use of the post-core maintenance curriculum. Future work will examine the effectiveness of GLB based on the type of curriculum and duration of the program.

Supported By: National Institute of Diabetes and Digestive and Kidney Diseases

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—GLUCOSE MONITORING AND SENSING

Frequency of Flash Glucose Monitoring Scans and Hemoglobin A1c in Real Life

ANDREA LAURENZI, AMELIA CARETTO, MARILUCE BARRASSO, ANDREA MARIO BOLLA, CHIARA MOLINARI, ANNA ZANARDINI, NICOLETTA C. DOZIO, ELENA MENESCHI, EMANUELE BOSI, MARINA SCAVINI, Milan, Italy; Consilvo Balsamo, Italy

Introduction: In patients with type 1 diabetes mellitus (T1D) the relationship between low number of self-monitoring of blood glucose (SMBG) measurements and elevated hemoglobin A1c (HbA1c) levels has been reported. However, the optimal frequency of SMBG has not been defined. Flash glucose monitoring (FGM) is an emerging technology allowing patient with diabetes to measure interstitial glucose concentrations in a non-invasive manner, with patients obtaining more measurements than with SMBG.

Materials and Methods: We collected data from 103 adult T1D patients using FGM technology in real life for at least 28 days. We recorded patients demographics, diabetes duration, type of treatment (CSII or MDI) and we downloaded FGM data to the Abbott Freestyle Libre software, which provides the number of daily FGM scans and estimates of HbA1c based on continuous glucose profile readings. The correlation between median FGM
scan frequency over 28 days and the estimated HbA1c was analyzed using Spearman rho. We also computed HbA1c median levels for quintiles of scan frequency and compared them using Kruskal-Wallis test.

Results: A significant correlation was found between median scan Spearman rho was -0.46 (p=0.0001). Moreover, median HbA1c level decreased significantly from the first (3-5) to the fifth (24-50) quintile of daily scan frequency ([69 mmol/mol (IQR 72 to 78) to 54 mmol/mol (49 to 50), p<0.0001] and remained unchanged thereafter, i.e., from the third to the fifth (24-50) quintile daily scan frequency ([54 mmol/mol (49 to 50) to 53 mmol/mol (45 to 56), p=0.7638]).

Conclusions: In T1D patients we confirmed that frequent measurements of interstitial glucose benefits glucose control in real life conditions. The maximum benefit in term of HbA1c decrease is obtained between 10 to 14 scans daily, a number of glucose measurements that would unlikely be sustainable with SMBG.

899-P

Associations between A1C and Continuous Glucose Monitoring-Derived Glycemic Parameters
PETER CALHOUN, TERRI JOHNSON, JOHN WELSH, TOMAS C. WALKER, DAVID A. PRICE, San Diego, CA

The percentage of continuous glucose monitoring (CGM)-derived sensor glucose (SG) values in the 70-180 mg/dL range (time in range [TIR]) is an important outcome for patients and their clinicians; however, consensus TIR goals are lacking. This study aimed to characterize associations between CGM-derived glycemic metrics and A1C in 4 clinical trials: DIAMOND Phase 1 (N=104), DIAMOND Phase 2 (N=69), REPLACE-BG (N=216), and HypoDE (N=141). Each study lasted ≥24 weeks, used current-generation CGM systems ( Dexcom, Inc.), and included comparisons of central-lab end-of-study A1C to CGM data during the preceding 3 mo. Data from 580 adults with diabetes (635 type 1) were analyzed. The Figure shows mean SG (mg/dL), TIR, time <70, <54, and ≥250 mg/dL; mg/dL, for individuals in 6 A1C bins. Higher A1C bins were associated with higher MSG and lower TIR; lower A1C bins were associated with lower MSG and higher TIR. For subjects with A1C ≥7.0%, median TIR was 72%, with 90% of subjects having TIR ≥57%. Median time with SG <54 mg/dL was <20 min/day for all A1C bins, but median time with SG ≥250 mg/dL increased from 0.6 h/day to 6.7 h/day across bins. For subjects with A1C ≥8.0%, median TIR was 44%, with 90% of the subjects having TIR <59%. In CGM users, low A1C values can be achieved with minimal additional exposure to very low SG values. The observed associations between TIR and A1C may help clinicians and patients establish appropriate TIR goals.

Figure.

900-P

Effect of Remote Glucose Monitoring Utilizing Computerized Insulin Dose Adjustment Algorithms on A1C Levels—A Preliminary Report
MAYER B. DAVIDSON, JOSH DAVIDSON, Los Angeles, CA

Adjusting insulin doses is very challenging for primary care physicians because of infrequent office visits and time constraints at the visit. For patients, frequent office visits are a barrier. We have used FDA-approved, computerized insulin dose adjustment algorithms and remote glucose monitoring to circumvent both of these issues. Diabetic patients in a safety net clinic who took insulin for at least 6 months with A1C levels ≥8.0% were enrolled in a study in which an iHealth glucose meter was attached to a smartphone containing an app downloaded from the Web that transmitted the glucose values to a secure, HIPAA-approved server. There the values were analyzed by the algorithms and a report with recommendations for dose changes was generated and sent to a clinic nurse practitioner every 2-3 weeks who could accept or modify the recommendations. A clinic staff individual contacted the patient with the insulin dose changes. Twenty-eight diabetic patients (one type 1) had reached 3 months. Their mean age (± SD) was 55.9 ± 8.6 years, 15 were females and 13 were males. There were 20 Latinos, 4 African-Americans, 3 Caucasians, and 1 Asian. Their insulin regimens were: basal alone - 11, basal/bolus - 14 and self-mixed/split - 3. No insulin drugs were not changed. Their baseline A1C levels (± SD) of 10.0 ± 1.2 decreased by 1.9 ± 0.9 to 8.1 ± 1.1 after 3 months. Their total insulin dose increased by 24%. There were no episodes of severe hypoglycemia (requiring 24th party assistance) nor severe hyperglycemia (requiring emergency room visit).

Conclusions: Remote glucose monitoring utilizing computerized insulin dose adjustment algorithms to analyze glucose values and generating recommendations for dose changes at more frequent intervals markedly improved A1C levels in poorly controlled diabetic patients in the absence of office visits.

901-P

Interim Analysis of an Implantable CGM System Longevity during a 365-Day Study
SURIN IOACARA, RAVI RASTOGI, COLLEEN MUNDI, XIAOQIAO CHEN, KATHERINE TWEDEN, Bucharest, Romania; Germantown MD

Background: Research has been conducted to extend the life of a subcutaneously-implanted CGM System (Eversense™, Sensonecs, Maryland U.S.A) using several strategies including the use of different configurations of an anti-inflammatory agent and improvement in glucose sensing and calculation methods. The current study investigated the longevity of the Eversense® XL CGM over the first 250 days of the planned 365-day evaluation period.

Methods: Thirty-four adult participants with T1D enrolled in a prospective, unblinded, single-center 365-day study. Sensors were inserted in the upper arm and assessed every 30-60 (±14) days for sensor longevity, safety and effectiveness. An interim analysis of sensor longevity was performed using the Kaplan-Meier method to estimate the probability of sensor survival through 250 days. CGM wear duration was also assessed to monitor subject compliance. Serious adverse events related to the device or removal procedures were assessed.

Results: Participant baseline demographics were 22 males/12 females, 30 ± 7.9 years of age, with BMI of 24 ± 3.6 kg/m² (mean ± SD). At this interim analysis, all sensors had a range of 124-365 days of use. Survival analysis at post-implant 90, 120, 150, 180 and 250 days showed an estimated probability of sensor survival of 97%, 94%, 84%, 80% and 51%, respectively. Median wear compliance was 231 hours/day (96% of time). No insertion, removal or device-related serious adverse events were reported.

Conclusions: The Eversense XL CGM demonstrated good survival and safety up to 250 days of sensor wear.

Supported By: Sensonics, Inc.
Benefits of Use of Professional CGM in Low Socioeconomic Population

SULMAN HASHMI, SANN MON, Mickeepa, PA

Introduction: Self-monitoring blood glucose (BG) using a glucometer is the standard of care for patients with diabetes. However, up to 67% of patients fail to routinely monitor BG, which is one of the major challenges to optimize glycemic management. With an emergence of technology, continuous glucose monitoring devices (CGM) are now used by many patients for guiding therapeutic changes. However, such technology is not always available in low socioeconomic areas.

Objective: To examine the ability of professional CGM for guiding therapeutic changes in a population with limited access to technology to improve glycemic control as measured by A1c, patient glucometer data, hypoglycemia events, and total daily insulin requirements before and after the testing period.

Method: Professional CGM (Freestyle Libre Pro) was placed for 10-14 days in 19 patients age ≥ 18 years (mean age 47.6 years +/- 19.6 SD, 58.42% female) with T1DM or T2DM on insulin therapy. CGM data was downloaded after the testing period, glucose results were retrospectively reviewed with the patient, and insulin dose adjustments were made.

Results: 66% of patients showed improvement in A1c with a median decrease of 0.8%. Mean A1c pre 9.2 and post 8.14 with the p value=0.13. Fewer hypoglycemic episodes and higher total daily use of insulin are noted in the post-CGM period. 7 episodes of severe hypoglycemic before and none following CGM use. There was an increase in the mean dose of insulin from 51.79 units to 56.93 units, p=0.14 post CGM. Statistically significant decrease in episodes of hyperglycemia Post CGM (Pre 11.66 to Post 7.31, p=0.03).

Conclusion: Professional CGM is useful for improving glycemic control in a low socioeconomic population with limited access to current technology. Despite a relatively small sample size, our study showed that there was an improvement in HbA1c and the decrease in the number of episodes of hyperglycemia and hypoglycemia after CGM placement.

A Feasibility Study to Detect Neonatal Hypoglycemia Using Real-Time Continuous Glucose Monitoring

LAURA M. NALLY, NICHOLAS W. BONDY, JASMINE DOIEV, BRUCE BUCKINGHAM, DARRELL WILSON, Stanford, CA

Introduction: Infants of diabetic mothers are at high risk of hypoglycemia (<47 mg/dl) after birth, with rates approaching 50% in the first 48 hours of life (HOL).

Methods: Infants born at ≥34 weeks gestation to mothers with diabetes had a CGM placed after birth and were remotely monitored by research staff during their hospitalization. Clinical staff and families were blinded to CGM data. For CGM readings <45 mg/dl, research staff requested a heelstick blood glucose (BG) using the hospital glucometer.

Results: Eleven infants were studied. Mothers had an average A1c of 5.6% (range 4.7-6.8%) prior to delivery and insulin requirement. Hypoglycemia (<45 mg/dl) was confirmed in 7 of 11 infants with 14 events at less than 12 HOL, 2 events between 12-24 HOL, and 1 event at >48 HOL. CGM detected hypoglycemia 4 times when the infant was not due for a BG check based on the standard of care. The true positive rate for sensor-detected hypoglycemia was 40% and the false positive rate was 80%. CGM detected 24% of the hypoglycemic events that the usual intermittent pre-prandial BG checks would have missed.
Clinical Diabetes/Therapeutics

**Poster 908-P**

**Intervention of the Flash Glucose Sensing Technology on Glycemic Control and Treatment Satisfaction in Patients with Type 2 Diabetes Treated Intensively by Insulin—A Randomized Controlled Trial**

**Authors:** JACE WEATHERLY, SANIYA S. KISHNANI, TANDY AYE, Palo Alto, CA, Stanford, CA

**Objective:** To determine the satisfaction from treatment and effectiveness of flash glucose monitoring system (FGM) in patients with type 2 diabetes.

**Design and Methods:** 101 individuals with type 2 diabetes on multiple daily insulin injection (MDI) therapy for ≥1 year (mean duration 21.81 ± 7.85 years) and HbA1c 7.4-10.2% (57-88 mmol/mol) were randomized to the intervention (n=50) or the standard care group (n=51). Those in the intervention group were instructed to use FGM and once a week 7-points BG assessment to confirm any a symptomatic hypoglycemia. The control group continued the routine BG measurement as before the study and add once a week 7-points BG measurement at constant day. For 12 weeks, both groups were instructed to adjust insulin dose in the frequent face-to-face and telephone contacts. Participants enrolled in MyChart, downloaded the HealthKit application and connected the AccuChek Aviva Connect (Roche) glucometer to the HealthKit. Through the EHR, BG values were automatically integrated to the EHR via WiFi. The number of patient initiated contacts via telephone or MyChart messages between clinic visits were recorded during each of the 3 phases (lasting 3 months each) run-in phase (providers waited for participant initiated phone calls), intervention phase (providers initiated calls to participants to review BG trends) and learned phase (providers waited for participant initiated phone calls). The number of participant initiated calls for each phase was measured and compared using a paired t test. Thirty-two families (mean Hgb A1c 8.5 ± SD 0.81%) did not improve. Families did feel safer knowing providers had automated integration of BG values into the EHR. However, barriers to adoption and effectiveness of this technology exist and patient motivation is still needed.

**Results:** The mean age was 66.75 ± 7.55; 64.35% were male. Total treatment satisfaction increased in the intervention group (p=0.055). At the 12 week of the study, subjects in the intervention group found treatment significantly more flexible (p=0.019), convenient (p=0.052), and would recommend it more to their counterparts (p=0.023). The mean HbA1c was 8.51 ± 0.81%. After 10 weeks, HbA1c changes were -0.82% in the intervention group and -0.29% in the control (p=0.001). 67.9% subjects from the intervention study and 39.6% subjects from the intervention and 16.7% from the control group reduced HbA1c ≥5.0% HbA1c (p<0.001); and 39.6% HbA1c ≥1.0% (p<0.001) without increasing frequency of hypoglycemia.

**Conclusion:** FGM potentially produces a modification of behavior/life style and improves treatment satisfaction. It improves glycemic control in subjects with type 2 diabetes treated by MDI without increased frequency of hypoglycemia.

**Supported By:** Abbott

**Poster 909-P**

**HbA1c Trends with Treatment Intensification following Inadequate Response to Two Oral Agents in Patients with Type 2 Diabetes**

**Authors:** KIBUN KIM, SUDHIR UNNI, DIANA BROKEN, SHEILA THOMAS, CODY J. OLSEN, KIMBERLY L. STERLING, MATT MITCHELL, CARRIE MCDAM-MARK, Salt Lake City, UT, Bridgewater, NJ, Murray, UT, Indianapolis, IN, Little Rock, AR

**Objectives:** To describe HbA1c trends 1-year post treatment intensification to insulin or noninsulin agents in patients with insufficient HbA1c control while on 2 oral antidiabetic agents (2 OADs).

**Methods:** A retrospective cohort study was conducted in a regional health plan claims database from 1/1/2010 to 3/31/2017. Included patients had type 2 diabetes (T2D) and their treatment was intensified with insulin, a GLP-1 receptor agonist (GLP-1RA) or a 3rd OAD within a year from an HbA1c ≥7.0% while on 2 OADs. HbA1c was estimated monthly by intensification with insulin or noninsulin (i.e., GLP-1RA and 3rd OADs) agents using a mixed-effect model.

**Results:** The study analyzed a total of 3,909 HbA1c measures from 1,226 patients. HbA1c reductions were significant, but most patients continued to have inadequate glycemic control (HbA1c ≥7.0%). Those receiving insulin had a higher baseline HbA1c (p<0.01), but showed more substantial HbA1c decrease vs. those intensified with a noninsulin agent (p<0.01), controlling for baseline HbA1c.

**Conclusion:** In patients with T2D, intensification following suboptimal glycemic control while on 2 OADs was associated with significant improvement in HbA1c control. Insulin intensification was associated with worse control at baseline, but greater HbA1c reduction than noninsulin intensification. Additional opportunity exists to improve glycemic control.

**Figure.**

**Supported By:** Sanofi U.S.
Comparison of Glycemic Control between Experienced Users of Flash Glucose Monitoring (Flash) by comparing Flash users to patients who use SMBG. We used the Glucose Monitoring Satisfaction Survey that consists of 15 items with a scale range of 1 to 5. 133 patients who were using Flash for 7.9 ± 9.5 months were compared with 83 patients who used SMBG since diagnosis. As a measure of between-group differences for each item, we compared the means using a t-test. The proposed method may become a useful tool for realization of noninvasive blood glucose prediction.

Near-Infrared Spectroscopic Method for Noninvasive Blood Glucose Prediction without Using Multivariate Analyses

A near-infrared spectroscopy method for noninvasive blood glucose prediction without using multivariate analyses is proposed and examined. Near-infrared diffuse reflection spectra with a wavelength range from 1400 to 1850 nm were measured at the skin tissue using an optical fiber probe. The difference spectra obtained by subtracting the initially measured spectrum from the other measured spectra were reconstructed from the spectra of four major components in the human skin (water, protein, glucose, and fat) and the spectrum of a scattering equivalent component called baseline, based on the modified Beer’s law. Then the blood glucose contents were predicted from the content index of the glucose component appearing in calculation of the reconstructed spectrum. We assumed that one of the origins of the errors in the blood glucose prediction using near-infrared spectroscopy was the similarity of the shapes of the absorption spectrum between glucose and baseline. To distinguish the glucose contribution from those of baseline and fat in the difference spectra, an imaginary component combining baseline and fat was introduced by considering that both the change in the fat contribution and the generation of baseline originated from the change in scattering in the skin. The imaginary component enabled us to reduce the errors in the blood glucose prediction. In contrast to the conventional methods using multivariate analyses, the calculation process of the proposed method is not so called “a black box.” Thus, it is easy to estimate the origins of the changes and contributions of the components in the difference spectra. The proposed method may become a useful tool for realization of noninvasive blood glucose prediction.

Effectiveness of real time continuous glucose monitoring (RT-CGM) compared with intensive self-monitoring of blood glucose (SMBG) is not clear. To analyze the effectiveness of RT-CGM, retrospective CGM and, intensive SMBG in adults with type 2 diabetes, we conducted a randomized, open-labelled clinical trial. Patients were type 2 diabetes adults admitted to our hospital from August 2016 to August 2017. Patients of age over 85 years, pregnant, admission less than 1 week were excluded. Patients were randomized to SMBG with RT-CGM using the Medtronic MiniMed 620G, SMBG with retrospective CGM using Medtronic iPro2, or SMBG alone. Both CGMs were worn for 6 days. SMBG was done 6 times a day at every pre-meal and 2 hours post-meal. Primary outcome was the change in HbA1c from baseline to 12 weeks. As the secondary outcomes, change in mean glucose level from the admission day to discharge day, and frequency of in-hospital hypoglycemia were evaluated. We also evaluated patients’ satisfaction to treatment using Diabetes Treatment Satisfaction Questionnaire (DTSQ). As the result, 111 patients were enrolled and 33 patients were allocated to RT-CGM group, 26 to retrospective CGM group, and 52 to SMBG group. Among these 111 patients, 63 (56.8%) were male, mean age was 65.1 years, diabetes duration was 8.3 years, BMI was 26.3 kg/m2, and HbA1c was 9.1%. Overall, glycemic control was improved after treatment for both HbA1c and the mean glucose level; HbA1c from 9.1±1.7% to 6.8±1.0%, mean glucose level from 189±56mg/dl to 137±19mg/dl. However, the changes were not significantly different between the groups. As the safety profile, 34 hypoglycemia were evaluated. We also evaluated patients’ satisfaction to treatment using Diabetes Treatment Satisfaction Questionnaire (DTSQ). As the result, 111 patients were enrolled and 33 patients were allocated to RT-CGM group, 26 to retrospective CGM group, and 52 to SMBG group. Among these 111 patients, 63 (56.8%) were male, mean age was 65.1 years, diabetes duration was 8.3 years, BMI was 26.3 kg/m2, and HbA1c was 9.1%. Overall, glycemic control was improved after treatment for both HbA1c and the mean glucose level; HbA1c from 9.1±1.7% to 6.8±1.0%, mean glucose level from 189±56mg/dl to 137±19mg/dl. However, the changes were not significantly different between the groups. As the safety profile, 34 hypoglycemia were seen during hospitalization with no difference in frequency between the groups (P=0.1). There were no differences in patients’ satisfaction to treatment assessed by DTSQ, either. In conclusion, among adults with type 2 diabetes, intensive SMBG may have the equivalent effect to RT-CGM and retrospective CGM.

Comparison of Satisfaction with Their Glucose Monitoring Device in Patients Using Flash Glucose Monitoring vs. Patients Using SMBG

Flash Glucose Monitoring offers several benefits to patients such as ease of use and no additional finger pricks. However, there are also some limitations that are being discussed such as perceived lack of accuracy and skin irritations. We analyzed different aspects of patients’ satisfaction with Flash Glucose Monitoring (Flash) by comparing Flash users to patients who use SMBG. We used the Glucose Monitoring Satisfaction Survey that consists of 15 items with a scale range of 1 to 5. 133 patients who were using Flash for 7.9 ± 9.5 months were compared with 83 patients who used SMBG since diagnosis. As a measure of between-group differences for each item, Cohen’s d was used to estimate the effect size. In general, Flash users were significantly more satisfied with how things were going with their diabetes (d = 0.31; p = 0.024). SMBG users indicated that measurement takes more time to use (d = 0.67; p < 0.001), makes them worry more (d = 0.32; p = 0.024), is more of a hassle to use (d = 0.45; p = 0.002), and is more painful to use (d = 0.55; p < 0.001) when compared to Flash users. Feeling frustrated with
SMBG data may aid clinical and educational approach to diabetes management for healthcare professionals (HCPs) and patients in the review of self-monitoring blood glucose (SMBG) data. SMBG was simultaneously put in place in 8 outpatients with type 1 diabetes. The disparity between the FGM SG values and the BG values varied greatly, with the MARD of FGM SG values and the durations of FGM put in place varied depending on the number of days FGM put in place. Additionally, the disparity between the FGM SG values and the BG values varied greatly depending on the individual patient.

Conclusions: While FGM represents an innovative device for glucose monitoring, there is a wide disparity between the FGM SG and BG values in some patients with type 1 diabetes, suggesting that FGM may be appropriately used as an adjunct, but not as an alternative, to SMBG.

Factors Associated with High Glycemic Variability Defined by Coefficient of Variation in Hypo-Prone Type 2 Diabetes

ANA MARIA GOMEZ, Bogota, Colombia

Objective: To determine clinical variables associated with high glycemic variability (GV) evaluated by continuous glucose monitoring (CGM) in patients with type 2 diabetes (T2D) and high risk of hypoglycemia.

Methods: A observational study with retrospective cohort analysis of the data was done. We included patients with T2D and history of hypoglycemia as an indication of CGM. GV was calculated using different metrics. They were classified depending on the coefficient of variation (CV) in 2 groups (<30% and ≥30%). Glycemia was defined as interstitial glucose levels lower than 54 mg/dL for at least 20 minutes. For possible association between clinical variables and the CV, we did a bivariate dichotomous logistic regression model, then for the construction of the multivariate model, all variables were included.

Results: 148 patients were included, 52 patients had hypoglycemia (35.1%), 52.0% were classified in the group with CV ≥30%. Three variables presented statistically significant differences: BMI comparing overweight vs. normal (OR 0.35; IC 95%, 0.16-0.78, p = 0.010) and obesity vs. normal BMI (OR 0.33; IC 95%, 0.16-0.66, p = 0.001). Notably, 89.3% of all glucose levels were lower for FSL-Pro than iPro2; therefore, the difference between them was considerable (Figure 1; r = -0.273, p < 0.01). The absolute difference between FSL-Pro and iPro2 glucose values was significantly higher among hyperglycemic values (>180 mg/dL) compared with normoglycemic values (70-180 mg/dL) (32.0 (19.0-47.0) vs. 23.0 (14.0-31.0) mg/dL, p < 0.05). We concluded that glucose values are lower when measured using FSL-Pro than iPro2 and this tendency became more pronounced under conditions of hypoglycemia.

Figure 1.
Glycated Albumin Correlates Better with A1C than Fructosamine as a Marker of Intermediate Glycemic Control—A Multicenter Prospective Trial

CYRUS DESOUZA, JULIO ROSENSTOCK, JUAN P. FRIAS, STANLEY HSIA, LYLE C. MYERS, ERIC J. KLEIN, RONG ZHOU, TAKUJI KOHZUMA, VIVIAN FÜNSÈCA, OmniHealth, NE, Dallas, TX; Los Angeles, CA; Huntington Park, CA; Lexington, KY; Olympia, WA; Cincinnati, OH; Tokyo, Japan; New Orleans, LA

To evaluate the clinical utility of Glycated Albumin (GA) as an intermediate-term marker of glycemic control (preceding 2 weeks), we compared the correlation and concordance of GA and fructosamine (FRA) with A1C and mean blood glucose (MBG) measurements. One hundred fifty-five subjects with type 1 (n=73) and type 2 diabetes (n=77) were assigned to Group 1 (n=98, A1C ≥7.5%, prescribed a change in diabetes therapy) and Group 2 (n=52, A1C <7.5%, remained on stable diabetes therapy). Fasting plasma glucose, GA, FRA, and A1C were measured at 0, 1, 2, 3, 4, 6, 8, 12, 16, 20, and 24 weeks. MBG was calculated using weekly 7-point self-monitored blood glucose (SMBG) profiles throughout the study. Continuous glucose monitoring (CGM) was conducted on 30 participants to confirm the accuracy of MBG calculated by SMBG. Across all subjects, GA correlation with FRA was 0.920; the minimum correlation was 0.863. The estimated mean correlations of GA with A1C and MBG were greater than that of FRA as estimated by mean Pearson correlations using the method of Lorenz. The within-subject correlation between GA and FRA was 0.643 and the correlations for GA and MBG were significantly greater than those observed for FRA (0.565 vs. 0.395 for A1C p<0.001; 0.548 vs. 0.413 for MBG, p<0.001). To further examine the concordance of GA with FRA and A1C and MBG, a comparison of the Pearson correlations demonstrated that in 56% of subjects GA had a higher correlation with both A1C and MBG than FRA, compared to only 4% of subjects where FRA had higher correlations with both. Overall, GA had a higher Pearson correlation with FRA and MBG in 82% and 70% of subjects, respectively.

In conclusion, GA may be a more useful diagnostic test than FRA in clinical situations requiring measurement of intermediate-term glycemic control.

Supported By: Asahi Kasei Pharma Corporation

Use of Automated Clinical Decision Support (CDS) to Effect Glycemic Control in Elderly Patients with T1D

GARRY M. STEIL, ADELOU O. OЛАДУНЈЈЕ, JONATHAN S. WALD, CHRISTINE SYLNE, АСТРИД ATАКОV-CАСТILLO, JORDAN GREENBERG, ТОРИ GREAVES, ЕЛЕНА ТОССИ, MEDHA MUNSHI, Boston, MA, Raleigh, NC

Older adults with T1D can require additional support to achieve glycemic goals as they may have cognitive impairment and be at high risk for hypoglycemia. The Technological Advances in Glucose Management in Older Adults Trial (TANGO) is a RCT comparing risk of hypoglycemia (primary outcome: time glucose <70 mg/dl per day) in patients older than 65 yo managed with pump or pen, randomized to receive CGM with automated CDS (intervention; INT) or equal clinical attention (control; CON). Patients are randomized after a 2-week period confirming ability to use CGM (2 successful insertions; Dexcom CGM) and baseline hypoglycemia (2 incidence of CGM < 70 mg/dl for 20 minutes). Sixteen subjects have been enrolled (median [IQR] age 70 [64 78] yo, all 16 eligible for randomization [9 pump and 4 pen patients randomized to INT, 3 to CON]). Insulin delivery, meal, and activity (FitBit) data are obtained daily from the cloud (glooko; see Figure) and an explicit CDS algorithm is used to review the data and recommend changes in CIR, ISF, and basal rates (pump patients), or long and short acting insulin doses (pen patients). CDS has reviewed 1194 days of patient data and generated 15 recommendations (average 1 every 78.6 days), all approved or modified. We conclude that hypoglycemia is common in this population and that patients can be managed with the aid of an automated CDS algorithm reviewing data at the end of each day.

Figure.

Supported By: National Institutes of Health

MiniMed™ Veo™ Insulin Pump Analysis for Real-World Nonadjunctive CGM Insights

BOYI JIANG, SADAF SOLEYMANI, ROBERT VIGERSKY, ASHLEY SULLIVAN, YUXIANG ZHONG, PRIATIK AGRAWAL, FRANCINE R. KAUFMAN, Northridge, CA

To assess glycemic outcomes during non-adjunctive use of a Medtronic continuous glucose monitoring system, CareLink™ personal software data were analyzed after insulin bolus delivery to correct hyperglycemia. Voluntarily uploaded data captured between January 1, 2015-August 12, 2016, from European users of the MiniMed™ Veo™ insulin pump with SmartGuard™ technology, were de-identified and analyzed. Non-adjunctive sensor glucose (SG) values were defined as manually-entered self-monitored blood glucose (SMBG) values that were within ±5 mg/dl of the preceding SG value. Non-adjunct vs. adjunct performance of the system in frequent non-adjunct users (at least, 10% non-adjunct use) was evaluated based on the frequency of post-correction blood hypoglycemia (made up of hypoglycemia (peak) over the 4 hours following insulin bolus delivery. All statistics were conducted per patient and analyzed using Wilcoxon signed rank test.

Among 23,784 total users, 5,851 were identified as frequent non-adjunct users. Of the over 1.7 million corrective boluses evaluated, 32% met the non-adjunctive criteria. Outcomes results are presented in the Table below.

The frequency and severity of hypoglycemia and hyperglycemia, although lower statistically with non-adjunctive vs. adjunctive corrective bolus delivery, showed likely clinical equivalency.

Use of Hyperpolarized (2-13C) Dihydroxyacetone to Detect Hepatic Gluconeogenesis

MATTHEW MERRITT, MUKUNDAN RAGAVAN, TATSIANA TSAROVA, Gainesville, FL

Diabetes afflicts millions of people worldwide and contributes to elevated risk of cardiovascular disease and stroke. Imaging of hepatic metabolic activity using MRI could prove advantageous for diagnosis, treatment monitoring, etc. With the advent of hyperpolarized (HP) carbon-13 based MRI, rapid imaging of metabolic flux is feasible without the use of ionizing radiation. In this work, we have utilized HP [2-13C]dihydroxyacetone (DHA) to observe hepatic metabolism in real time in a perfused mouse (C57BL/6J) liver model. We have utilized fatty acids and a 1:10 ratio of pyruvate to lactate in the perfusate to mimic physiological conditions. Figure 1 shows the various metabolites observed following the injection of DHA. Ratios of integrals of three-carbon intermediates and hexose sugars (and phosphates) are used to determine the rate of gluconeogenesis. Hepatic gluconeogenic rates are measured in parallel with gold standard tracer methods, confirming the accuracy of HP imaging.

921-P

Clinical Diabetes/Therapeutics

920-P

Clinical Diabetes/Therapeutics

922-P

Clinical Diabetes/Therapeutics

Table.

<table>
<thead>
<tr>
<th>Threshold</th>
<th>Frequency in Hypo/Hyper Ranges Following Corrective Bolus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Adjuvant</td>
<td>SMBG Bolus Median [IQR]</td>
</tr>
<tr>
<td>&lt;54 mg/dl</td>
<td>0.0% [0.0, 1.0]</td>
</tr>
<tr>
<td>&gt;70 mg/dl</td>
<td>25.5% [18.2, 33.3]</td>
</tr>
</tbody>
</table>

For all three comparisons, p<0.001.
The New Smartphone Application for Blood Glucose Monitoring (BGM) with Information-Motivation-Behavioral Skills (IMB) Model Study

SCOTT PARDO, SERGEY ZHULETAV, JANE WALLACE, TIMOTHY S. BAILEY, Panippany, NJ, Escondido, CA

The accuracy of the CONTOUR® NEXT ONE BGM system (BGMS), which includes a wireless-enabled BG meter that links to the CONTOUR® Diabetes app installed on a mobile device. The CONTOUR® Diabetes app Version 2 Prototype detects repeated behavioral patterns in testing results and reports them back to the user. By decision of the user, recommendations are triggered to help with elimination of conditions related to the diagnosed pattern. The goal of the interactive app interface implementation is to achieve behavioral change in people with diabetes for better adherence to treatment and sustained glycemic control. The app employs messaging via the IMB model. A 6-week study with 46 insulin-using people with diabetes was performed to assess operational parameters and user reactions to the system. Analyses were performed on glycemic variables, such as fructosamine levels and HbA1c, and on subject questionnaires. Fructosamine levels decreased significantly from the beginning to the end of the study (P < 0.0076). All but 1 subject had IMB patterns detected, ranging from messages relating to “running low” to “pre-dinner high.” “Critical High” was the most frequently detected pattern. A multivariate cluster analysis, based on questionnaire responses only, revealed that subjects could be classified into one of two clusters based on their responses to the app. The only demographic or diabetes history variable significantly related to cluster membership was diabetes type. One cluster included only subjects with type 1 diabetes; the other cluster was a mix of both diabetes types. To further evaluate the benefits and efficacy of IMB as it relates to glycemic control, a larger study following subjects over a longer time period is required.

Support: Ascension Diabetes Care

Use of the New Smartphone Application for Blood Glucose Monitoring (BGM) with Information-Motivation-Behavioral Skills (IMB) Model Has an Impact on Diabetes Control Parameters

SCOTT PARDO, SERGEY ZHULETAV, JANE WALLACE, TIMOTHY S. BAILEY, Panippany, NJ, Escondido, CA

The accuracy of the CONTOUR® NEXT ONE BGM system (BGMS), which includes a wireless-enabled BG meter that links to the CONTOUR® Diabetes app installed on a mobile device, has been shown in previous studies. The CONTOUR® Diabetes app Version 2 Prototype detects repeated behavioral patterns in testing results and reports them back to the user. The user can choose to receive recommendations to help eliminate conditions related to the diagnosed pattern. The goal of the interactive app interface implementation is to achieve behavioral change in people with diabetes for better adherence to treatment and sustained glycemic control. The app employs messaging via the IMB model. A 6-week study with 46 insulin-using people with diabetes was performed to assess operational parameters and user reactions to the system. Further to pre-protocol analyses, some post-hoc analyses were performed. In addition to a significant decrease in fructosamine level from the beginning to the end of the study (per-protocol analysis), there was a significant decrease in the number of above-target (“high”) blood glucose measurements per week per subject (P < 0.0001). This result may be related to a decrease in extreme glycemic fluctuations. The average number of blood glucose tests performed per week increased significantly over the course of the study (P < 0.0001), indicating the potential effects of using the system on encouraging patient adherence to treatment and better control of blood glucose levels. While not statistically significant, the average blood glucose values for fasting, before meal, and after meal consistently decreased. A larger study following subjects over a longer time period is required to evaluate the benefits and efficacy of IMB as it relates to glycemic control.

Support: Ascension Diabetes Care
A Novel Composite Glucose Index (COGI) for Evaluating Closed-Loop Performance in Type 1 Diabetes

LALANTHA LEELARATHNA, HOOD THABIT, LIA BALLY, MALGORZATA E. WILINSKA, JULIA K. MADER, THOMAS R. RIEBER, MARK EVANS, RUMANI HOUVRKA,
Manchester, United Kingdom, Berne, Switzerland, Cambridge, United Kingdom, Graz, Austria

Presently, no single index exists that summarizes key aspects of continuous glucose monitoring (CGM) data. Such an index may be useful in evaluating outcomes in closed-loop (CL) as well as other novel diabetes technology studies utilizing CGM. Here we present a novel composite glucose index (COGI), encompassing three key elements of CGM (Table). The total index ranges from 0 to 100, where 100 approximates glucose profile of people without diabetes. One percent reduction of time <70mg/dL is equivalent to 4.7% increase in time in range (TR) and 9mg/dL reduction in standard deviation of CGM is equivalent to 3% increase in TR. We used the COGI to assess the incremental benefits of day-and-night hybrid CL on glucose control compared to insulin pump therapy during a previously reported randomized cross-over, 4-week study in adults with well-controlled type 1 diabetes (n=28), mean, baseline HbA1c 6.3% (52 mmol/mol), age 41 years, duration of diabetes 24 years. Mean (SD) of CGM was 80.0(11) (range 41 to 81) during the control period, which improved to 75 (7) (range 58 to 86) during CL (paired difference: +15, p<0.0001, 95% CI +11 to +18). We demonstrate a novel composite glucose index based on CGM which improved considerably during CL, even in people with optimal HbA1c. A composite CGM-based metric may thus have a role in evaluating glyemic control attributable to CL and other novel technologies beyond HBa1c.

Table. Composition of the COGI and Relative Contributions of Its Three Components.

<table>
<thead>
<tr>
<th>Glucose Area</th>
<th>CGM metric</th>
<th>Relative scoring</th>
<th>Relative Contributions to COGI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in range (TR)</td>
<td>Percent time spent between 70 to 180mg/dL</td>
<td>TIR from 0% to 100% where 0% TIR is given 0 points and 100% TIR is given 100 points</td>
<td>50</td>
</tr>
<tr>
<td>Time in hypoglycemia (TH)</td>
<td>Percent time spent below 70mg/dL</td>
<td>TIR from 0% to 15% where 15% TIR is given 0 points and 100% TIR is given 100 points</td>
<td>35</td>
</tr>
<tr>
<td>Glucose variability (DV)</td>
<td>Standard deviation (SD)</td>
<td>SD from 18 to 180mg/dL where 15 SD is given 0 points and SD 180mg/dL and below is given 100 points and SD 180mg/dL and above is given 0 points</td>
<td>15</td>
</tr>
</tbody>
</table>

Supported By: University of Manchester, JDRF; UK National Institute for Health Research, Cambridge Biomedical Research Centre; UK Wellcome Trust (100574/Z/12/Z); Swiss National Science Foundation (P1BEP3_165297)

Effectiveness and Tolerability of Vildagliptin plus Metformin Compared with Other Oral Dual Antidiabetic Agents in Different Baseline HbA1c Patients with Type 2 Diabetes—A Real-World Study (China PDS)

DAGING HU, YING HAN, LIXIAN CHEN, HUI JIN, NAILONG YANG, XIAOYUN SHI, QUANMIN LI, LINLIANG LIANG, LI ZANG, MINGMINI LUI, JAMES HE, YIMING MU, WUHAN, China, Tianjin, China, Nanjing, China, Qingdao, Beijing, China, Shenyang, China, Shanghai, China

Background and Aim: China PDS aimed to investigate the real-world effectiveness and tolerability of vildagliptin plus metformin (VM) in patients with type 2 diabetes mellitus (T2DM), compared with other oral dual agents (OD). Here, we present the results of prespecified baseline HbA1c subgroups. Materials and Methods: In China PDS, T2DM patients with poor glycemic control by monotherapy were assigned to either VM dual therapy or OD therapy according to local physician’s decision. In this subgroup study, patients were divided into three groups according to their baseline HbA1c levels (<8%, 8-9%, >9%). The primary outcome was the proportion of patients with HbA1c <7% and without tolerability events (hypoglycemia, weight gain, or discontinuation due to gastrointestinal event) at 12th month. Secondary outcomes included mean changes in HbA1c from baseline to study endpoint and tolerability.

Results: In total, 706 (312 in VM vs. 394 in OD) patients in HbA1c <8% group, 332 (151 in VM vs. 181 in OD) patients in HbA1c 8-9% group, and 236 (141 in VM vs. 95 in OD) patients in HbA1c >9% group were enrolled. Compared with OD, significantly higher proportion of patients reached primary outcome with VM in HbA1c <8% group (57.4% vs. 38.3%, P=0.001), in HbA1c 8-9% group (59.7% vs. 26.0%, P=0.001), and in HbA1c >9% group (48.2% vs. 31.6%, P=0.011). The mean HbA1c changes from baseline to study endpoint in VM and OD were -0.61±0.932 and -0.32±0.874 (P=0.001) in HbA1c<8% group, -1.37±1.072 and -0.97±1.169 (P<0.001) in HbA1c 8-9% group, and -2.71±1.392 and -2.39±1.406 (P=0.005) in HbA1c>9% group. Compared with OD, VM resulted in less tolerability findings (HbA1c<8%: 7.7% vs. 16.8%; HbA1c 8-9%: 2.6% vs. 9.4%; HbA1c>9%: 5.0% vs. 18.8%; P=0.05 for all).

Conclusion: In different baseline HbA1c groups, vildagliptin plus metformin dual therapy was associated with better glycemic control and good tolerability.
**930-P**

**A Wireless, Integrated, Extremely Miniaturized Continuous Glucose Monitoring System**

MUHAMMAD MUJEEB-U-RAHMAN, MISEAM HONARVAR NAZARI, MEHMET SENCAN, Irvine, CA

Miniaturization is a key performance driver for CGM sensors for diabetes management. We have combined semiconductor and nanotechnology to realize an extremely miniaturized (0.1mmx0.8mmx3mm i.e., smaller than a sesame seed) fully wireless implant for electrochemical glucose sensing in interstitial fluid. This small size minimizes foreign body response, thus increasing longevity and decreasing calibration frequency. The implant is inserted under the skin using a custom injector and is removed via a simple procedure under local anesthesia. The implant is powered via an external wearable transmitter using standard RFID technology, also enabling low power communication between the two. The transmitter uses a Bluetooth link to communicate with a smartphone reader for data visualization and further analytics. The smartphone sends data securely to an online database where it is shared with caregivers.

We have verified our digital health system’s operation through extensive in-vitro and in-vivo testing (Figure). We have de-risked sensor fabrication and sterilization schemes. The wound healing response and histopathology studies indicate favorable safety and biocompatibility profile for the sensor as it uses standard materials being used in other implants. We are optimizing glucose oxidase system’s chemistry to achieve optimal in-vivo performance leading to human feasibility testing.

---

**931-P**

**Mobile Technology for Behavioral Feedback on Glycemic Excursions—A Qualitative Study**

MARIYAN D. RUTHOLZ, OWEN HENN, ASTRAI ATAKOV-CASTILLO, LAWRENCE FISHER, ELENA TOSCHI, Boston, MA, San Francisco, CA

Little is known about how adults with type 1 diabetes (T1D) engage with technology to make changes in diabetes self-management. We explored the qualitative experiences of T1D adults after a clinical intervention that included FreeStyle Libre (FSL) linked to “Sugar Sleuth,” a mobile-based system that prompted patients to reflect on the causes of daily glycemic excursions in real time. Ten T1D adults (baseline A1c 8.0% ± 0.4; 60% male, 52±16 years old, T1D duration 31±14 years, 40% insulin pump) met with clinicians 5 times over 14 weeks initially to learn to use Sugar Sleuth and then to collaboratively review glucose data. They also completed an online nutrition education module focused on the impact of food on post-prandial glycermia. Research psychologist conducted semi-structured interviews that were transcribed, coded, and analyzed using content analysis to derive themes. Three main themes emerged regarding the integrated FSL + Sugar Sleuth system: Empowering Tool, provided constant information for diabetes management, could be used to discuss with clinicians; Psychosocial Support, promoted a sense of normalcy and relief from worry, and aided diabetes coping; Approaches to Glycemic Data, 50% described using FSL + Sugar Sleuth to review data, problem-solve, understand cause and effect, and plan for future self-care; the remainder focused only on immediate glucose numbers, trend arrows, and graphs but rarely reviewed data retrospectively. At study end, A1c was reduced by 0.4±0.14% (P<0.005) without a significant change in total daily insulin dose.

Overall, participants perceived distinct benefits from this intervention, which incorporated the use of FSL + Sugar Sleuth and clinical support to facilitate changes in diabetes self-management. These qualitative results are supported by improvement in A1c. Further study of FSL + Sugar Sleuth can inform more personalized clinical and mobile-based interventions for T1D adults.

Supported By: National Institutes of Health; National Science Foundation

---

**932-P**

**Randomized, Multicentric, Prospective Study Assessing the Effect of Adding Vildagliptin to Insulin in Hemodialysed Type 2 Diabetic Patients—The VILDDIAL Study**

MARION MUNCH, AGNES SMAGALA, LAURENT MEYER, NICOLAS MEYER, COIDLE VERIER, DOMINIQUE I. FLEURY, SR. BRUNO GUEBC, THIERRY HANNEDOUCHE, JOELLE CREDOIG, SR. PHILIPPE BALTZINGER, DIDIER DUCLOUX, SOPHIE BOROT, KRISTIAN W. KUNZ, FARIDHE ALENAH, PATRICE WINISZEWSKI, FRANCOIS CHANTREIL, LAURENCE KESSLER, Strasbourg, France, Colmar, France, Valenciennes, France, Vandœuvre-lès-Nancy, France, Besançon, France, Mulhouse, France

Introduction: Type 2 diabetic patients (T2D) undergoing chronic dialysis are at very high cardiovascular risk, requiring optimization of insulin treatment. Vildagliptin (Galvus), can be used in severe and terminal renal impairment (eGFR<30 or <15ml/min/1,73m²) and protects against hypoglycemia. The aim of this study was to evaluate the efficacy and safety of vildagliptin (50 mg/d) on top of insulin in hemodialysed T2D.

Methods: Sixty-five patients treated with multiple daily insulin injections were randomized (group 1-G1, n=33 usual insulin regimen, group 2-G2, n=32-addition of vildagliptin) in a multicentric, prospective, controlled, open-label, 12 weeks- study. Glucose control was evaluated using Continuous Glucose Monitoring (CGM, I-Pro Medtronic) for 48h, at Week 1 (W1) and Week 12 (W12). HbA1c and daily insulin needs. Statistical analysis was performed in intention to treat.

Results: Both groups were comparable (G1 vs. G2) for age (71.3 ± 7.4 vs. 69.7 ± 9.0 years), BMI (21.2 ± 6 vs. 24.5 ± 6.4 kg/m²), daily doses of insulin (47.7 ± 22.9 vs. 51.3 ± 25.4 mg), HbA1c (7.3 ± 1.1 vs. 7.3 ± 1.1%), and mean glucose at W1 (using CGM, 167.6 ± 58.3 vs. 149.4 ± 76.1 mg/d). At W12 compared to W1, mean glucose decreased significantly only in G2 (149.4 to 136.6 mg/dl, p<0.05). At W12 in G2 vs. G1, time in range (70-180 mg/dl) was lower in G2 vs. G1, and no significant difference was observed in microalbuminuria levels (p=0.62).

Supported By: Abbott

---

**932-P**

**Adults with Type 1 Diabetes (T1D) Using Continuous Glucose Monitoring (CGM) Report Disease Has Little Impact on Daily Functioning—T1D Exchange**

LUJI FAN, COLLEEN GARY, JINGWEN LIU, BETH MITCHELL, JEFFREY BISHAM, ALICIA H. MACLURE-FOGARTY, Indianapolis, IN, Boston, MA

Glycemic Variability (GV) and Treatment Satisfaction (TS) are not accurately reflected in HbA1c. This study explored GV measures and their effect on insulin TS, productivity and activity in a real-world population with T1D.

This prospective survey was of 98 adults from the T1D Exchange online patient community. Surveys were completed and CGM data were downloaded at baseline and weekly thereafter for 4 weeks (week). The Insulin Treatment Satisfaction Questionnaire was done at week 4, and Work Productivity and Impairment (WPI) and Activity Impairment (AI)-General Health Questionnaire were done weekly for 4 weeks. Linear regression and mixed models explored the relationship between GV and TS, and impairment, respectively. Overall mean age was 43 years (SD 15.3), mean years with T1D was 22 (SD 14.2), 68% were female, and mean self-reported most recent HbA1c was 6.8% (SD 0.8). Participants on insulin pump (n=88) and multiple daily injections (n=12) took an average of 47.3 Units (±3.68) and 39.3 Units (±23.1) of insulin, respectively. Markers of GV and patient reported measures are in Table. Of the 14 GV measures examined, CV and LBGI showed a positive association with insulin TS (p<.05). No GV measures significantly impacted WPI or AI. The adult population with T1D in this survey had high TS, and had low WPI and AI, despite overall moderate risk for hypoglycemia.

Supported By: Abbott

---

**Poster Discussion**

**ADD-Supported Research**
greater (77.2 vs. 69.5%, p < 0.05). Time spent >180 mg/dL was lower (21.27 vs. 39.03%, p < 0.05), there was no difference in time spent <70 mg/dL (1.54 vs. 1.45%, NS). At W12, HbA1C and insulin requirements were respectively 6.9±0.9% vs. 7.2±1.1% (NS) and 49±32 IU/d vs. 46±23 IU/d (NS). There was no difference in adverse events between both groups. Overall, 8 symptomatic hypoglycemia occurred in D1 and 13 in G2.

Conclusion: Adding vildagliptin (50 mg/d) to insulin in hemodialysed T2D improves glycemic control by increasing time spent in normoglycemia and reducing time in hyperglycemia, without increasing time in hypoglycemia.

934-P

Relationship between Frequency of Blood Glucose Testing and Reduction in HbA1C and Body Weight during Intensive Lifestyle Intervention in Patients with Type 2 Diabetes and Obesity

SHAREE TOMAH, NOOR MAHMOUD, ADHAM MOUTALIB, KHALED ALSIBAI, SAHAR ASHRAFZADEH, TARA ELSEAYDI, OSAMA HAMDY, Boston, MA.

Self-monitoring of blood glucose (SMBG) is known to be valuable for proper diabetes management. However, the optimal frequency of SMBG has been debated. The aim of this study is to evaluate the relationship between frequency of SMBG and the degree of glycemic control and the magnitude of weight reduction in patients with type 2 diabetes (T2D) and obesity enrolled in an intensive lifestyle intervention (ILI).

We evaluated 38 patients with T2D and obesity (mean age 56±9 years, 56% female) enrolled in the Weight Achievement and Intensive Treatment (Why WAIT) program, a 12-week multidisciplinary ILI clinical program between May 2016 and December 2017. Participants were asked to test their blood glucose before each meal, at bed time, before and after exercise, occasionally postprandial and when needed. At baseline, average body weight was 105.7±20.9 kg, BMI 36.8±kg/m², HbA1C 7.8±1.3% and 41% of participants were treated with insulin. Based on their actual frequency of SMBG per day, participants were divided into tertiles. The lowest tertile tested on average 2.3±0.6 times/day (range: 1.1–2.9 times). The middle tertile tested on average 3.3±0.3 times/day (range: 3.0–3.9 times). The highest tertile tested on average 5.2±1.4 times/day (range: 4.0–7.7 times). HbA1C and body weight did not differ between tertiles at baseline.

At 12 weeks, HbA1C changed by -0.8±0.3% (p=0.01), -1.0±0.3% (p=0.01) and -1.7±0.5% (p=0.001) respectively from baseline. Body weight changed by -7.6±3.2 kg (-7.13%), -9.2±6.4 kg (-8.7%), and -10.6±4.1 kg (-9.9%) respectively from baseline (p<0.01 for all). The reduction in HbA1C and body weight was significantly better in the highest tertile of SMBG in comparison to the lowest tertile (p=0.05 for both).

In conclusion, patients with T2D and obesity who test their blood glucose more often during ILI achieve significantly better HbA1c reduction and significantly higher percentage of weight loss.

935-P

Performance of the GLUCOCARD® Shine XL Blood Glucose Monitoring System Compared with FDA 2016 Guidance Accuracy Criteria

JULIE WALKER, PATRICIA GILL, DANIELLE MAHER, JOHN M. GLEISNER, Minneapolis, MN; EDTA, MN.

Background: Blood Glucose Monitoring Systems (BGMS) are important tools used in the management of diabetes mellitus. Accurate BGMS readings are needed to prevent potential micro and macrovascular complications due to uncontrolled blood glucose levels. The FDA’s 2016 Guidance, “Self-Monitoring Blood Glucose Test Systems for Over-the-Counter (OTC) Use,” is FDA’s recommendation for measuring the accuracy of OTC BGMS. The accuracy boundaries of the guidance require that 95% of all results fall within ±15% of reference and 99% within ±20% of reference.

Purpose: This study evaluated the GLUCOCARD® Shine XL BGMS performance against the accuracy boundaries set by the FDA’s 2016 Guidance.

Methods: Three lots of test strips were evaluated in a side-by-side comparison at the ARKRAY Factory in Minneapolis, Minnesota. Blood samples were drawn from the fingertip of people with diabetes (n=180) by trained laboratory professionals between November and December 2017. Reference values were obtained using the YSI Model 2300 Analyzer. Data was evaluated against the accuracy boundaries of the FDA’s 2016 Guidance for Self-Monitoring Blood Glucose Test Systems for OTC Use.

Results: 98.3% (177/180) of the combined results for the three lots of GLUCOCARD® Shine XL BGMS fell within ±15% of reference and 99.4% (178/180) were within ±20% of reference. Overall bias was 2.2% and the correlation coefficient was 0.99 [r].

Conclusion: The GLUCOCARD® Shine XL BGMS performed within the accuracy boundaries of the FDA’s 2016 Guidance, Self-Monitoring Blood Glucose Test Systems for OTC Use.

936-P

Fourth-Generation Glucose Sensor with an Advanced Algorithm Featuring No Calibrations and Optional Calibration Modes of Operation

TALY ENGEL, PETER AJEMBA, JEFFREY NISHIDA, KEITH NOGUEIRA, BENYAMIN GROSSMAN, ANDY TSIAL, YUNFENG LU, ASHLEY SULLIVAN, ANDREA VARSASKY, Northridge, CA.

An advanced algorithm was developed for the Medtronic fourth-generation glucose sensor to eliminate the need for blood glucose meter calibrations. The algorithm uses electrochemical impedance spectroscopy and other measurements to self-calibrate the sensor and adjust CGM system sensitivity over time. Self-calibration adjusts for potential sensor-to-sensor variability, as well as subject-dependent sensitivity changes over time.

The new algorithm was designed to not require self-monitored blood glucose (SMBG) input during use, but accepts calibrations at any time to improve CGM system performance. It contains multiple independent sensor glucose (SG) calculation units that implement a distinct dynamic model of interstitial glucose that accounts for differences in response caused by sensor-dependent and time-dependent nonlinearities. This approach is particularly useful during the post-sensor insertion period and during periods of hypoglycemia. Each dynamic model was selected for its unique pattern of strengths, which complement each other to augment overall performance. The output of each model is combined to provide a final SG value and a measure of confidence in the calculated value.

Performance was evaluated on 31 subjects with type 1 and type 2 diabetes from SMBG values (2441 points over 80 sensors). Sensors were inserted in the arm. The (7-day) mean absolute relative difference was 10.8% with no calibrations, 9.5% with 1 calibration/day. There were 86.7% of points that met the 20% agreement rate with no calibrations, 90.0% with 1 calibration/day.

A new advanced algorithm for the fourth-generation glucose sensor enables the CGM system to function with good accuracy without SMBG calibrations.

937-P

Adaptive Modeling of Glucose Measurements with Unannounced Meals and Exercise

IMAN HAJIZADEH, MUDASSIR RASHID, ALI CINAR, Chicago, IL.

Reliable artificial pancreas (AP) systems require accurate models of the glucose-insulin dynamics in people with type 1 diabetes mellitus (T1DM). The realization of a fully automated AP system, however, is not possible with manual user entries for meals and exercise. To promote the development of automated AP systems without any user inputs, an adaptive and personalized data-driven model is developed that characterizes the evolving glycemic dynamics of individuals while explicitly considering the estimated effects of unknown disturbances such as meals and exercise. To achieve this adaptive and personalized modeling approach that best describes the glucose dynamics at any given instant without manual user input, we first quantify the effects of the unknown meals through adaptive estimates of time-varying parameters in a dynamical physiological model. The evaluated meal effects are incorporated with plasma insulin concentration estimates and readily measured physiological data from noninvasive sensors, such as heart rate and energy expenditure, to determine the overall state of the individuals. The proposed modeling approach integrates first-principles physiological models and data-driven empirical techniques to determine an accurate and comprehensive perspective of the individual at any given time. Simulation case studies involving in silico subjects from the U.S. Food and Drug Administration approved University of Virginia/Padova metabolic simulator demonstrate the improvement in prediction ability of the proposed approach. The root-mean-square error and mean absolute error for 30-, 45-, and 60-min-ahead predictions are 15.61 and 8.98 mg/dL, 21.82 and 13.49 mg/dL, and 25.96 and 17.00 mg/dL, respectively. The accurate predictions of future glucose concentration measurements without requiring manual user inputs will enable fully-automated AP systems that perform efficiently by maintaining euglycemia and mitigating glucose excursions.

Supported By: National Institutes of Health, JDRF.
938-P

Improvement of Glycemic Control after Three Months’ Use of the Predictive Low-Glucose Management System and Persisting for 18 Months in Patients with Diabetes Mellitus Type 1

TIRANTAYFOS IDANGELOS, PARTHENA GIANNOULAKI, ELENI KARLAFI, EVANGELIA KOTZIANOULI, Zsis KONTINANIAS, Konstantinos Tziomilos, Apollos Io Hatzizotos. Thessaloniki, Greece

Aim: To study the efficacy of the Medtronic Minimed 640g insulin pump (CSII with Suspend before low [Predictive Low-Glucose Management (PLGM)] on glycemic control in patients with diabetes mellitus type 1 (DM1T1) at baseline, after the first trimester and after 18 months’ use.

Methods: Thirteen patients with DMT1 participated who were on PLGM system (Minimed 640g system-Medtronic), 8 females, age 45.8±12.5 years, DM duration 28.1±8.5 years and PLGM duration 17.5±7.4 months. HbA1c, anthropometric measurements and medical history were recorded at baseline, after 3 months and after 18 months’ use of the PLGM system. The continuous glucose measurements (CGM) data of the last two weeks of each interval were downloaded using the software Carelink Pro and Personal.

Results: The glycemic control after using PLGM system was significantly better compared with baseline at 3 and 18 months’ use (HbA1c, 7.2±0.7% vs. 6.6±0.5 vs. 6.7±0.5, p = 0.006). There was an improvement at first trimester compared with baseline (HbA1c, 6.6±0.5 vs. 7.2±0.7, p = 0.027), and at 18 months compared with baseline (HbA1c, 6.7±0.5 vs. 7.2±0.7, p = 0.046).

There was no difference in glycemic control between 3 and 18 months use. There was no difference of time duration > 9.9 mmol/l (min/day), hypoglycemic episodes and AUC < 3.9 mmol/l compared with baseline at 3 and 18 months use. There was a reduction of the time duration > 9.9 mmol/l (min/day) between baseline and after 18 months use (3281.3±2175.9 vs. 1891.6±555.7, p = 0.037).

Hyperglycemic events were reduced significantly after 18 months compared to baseline (median 28.5, interquartile range (IQR) 14 vs. median 39.5, IQR 19, p = 0.045).

Conclusion: Patients with DMT1 using CSII with PLGM system for 18 months improved their glycemic control due to the reduction of hyperglycemic fluctuation. Glycemic control improved after 3 months and that improvement persisted for 18 months of follow-up.

939-P

Intermittently Scanned Continuous Glucose Monitoring (iscGM)—Examination in Pediatric Patients With and Without Ketoadiposis

GABRIELA A. BONI, MICHAEL WURM, BARBARA C. HANSEN, KARI, OTFRIED SCHWAAB, Tampa, FL, Freiburg, Germany

The iscGM (FreeStyle Libre “flash”) is approved in a number of countries for use in adults, but has had minimal study in pediatric groups and no reports of its use during ketoadiposis. This study in pediatric patients sought to compare paired sampling from this iscGM to the AccuCheck Aviva glucose monitor under conditions of varying glucose levels and varying degrees of ketoadiposis.

Twelve hyperglycemic T1D patients, ages 6-16 years, were studied with a minimum of 16 paired comparisons in each condition: 3 with ketoadiposis (pH 7.2-7.3) and one with severe ketoadiposis (pH <7.2), and all others nonketotic. Up to a 15% measurement difference between BG and tissue glucose measurements for BG > 100 mg/dl, or an absolute difference of 15 mg/dl for BG < 100 mg/dl were considered within target range. Blood glucose levels ranged from 35 to 556 mg/dL (1.94-30.89 mmol/L) and pH levels 6.9 to 7.6. Mean absolute relative differences (MARD, iscGM vs. Accucheck paired measurements) were: 426 non-ketoacidotic with BG >100 mg/dL: MARD of 11.77% with 69.2% of values within a 15% difference; 96 non-ketoacidotic with BG < 100 mg/dL: MARD of 12.4% with 78.1% within 15%, 17 ketoacidotic with BG>100 mg/dL: MARD of 12.4% with 70.6% within 15%, and 6 severely ketoacidotic with MARD of 22.68% with 16.7% within 15%, constituting a major difference with severe ketoacidosis. Clarke Error Grid Analysis for results with non-ketoacidotic values with BG <79 mg/dL: 93% in Zone A and 7% in Zone B; ketoacidotic values: 94.11% in Zone A and 5.89% in Zone B; and severely ketoacidotic values: 55% in Zone A and 55% in Zone B. Of the 545 paired comparisons obtained, only 17 were obtained during ketosis and 6 during severe ketoacidosis. These results show that this “flash” is iscGM and BG measurements determined by AccuCheck Aviva are highly concordant, however, the major differences observed during severe ketoacidosis urge caution in interpreting the blood glucose levels under this condition.

940-P

Use of the Tidepool Platform to Collect, Integrate, and Visualize Diabetes Device Data in a Pediatric Clinic Setting

JENICE C. WONG, ZARA IZADI, SHANNON M. SCHROEDER, MARIE NADER, HUOJIN J. MIN, AARON B. NEINSTEIN, SALEH ADI, San Francisco, CA

Glucose meters, insulin pumps, and continuous glucose monitoring systems provide data needed for pediatric type 1 diabetes patients to adjust insulin doses, modify their treatment regimens, evaluate lifestyle changes, or troubleshoot unexpected glucose levels. Health care providers (HCPs) can use device-specific software to review data at patient visits, often using separate, proprietary applications for each device. Using mixed qualitative and quantitative methods, we examined the feasibility of using the Tidepool platform and web application to view diabetes data from multiple devices together, in a multidisciplinary pediatric diabetes center where it was standard practice to upload and view data using device-specific software for each patient visit. Participating HCPs (n=15) used the software with compatible devices in all patient visits for 6 months. To evaluate the effect of the application on workflow, registration desk activity and office visits were observed before and after introducing the software, and HCPs provided feedback by survey and focus groups. The time required to upload device data and the length of the office visit did not change. However, the number of times the provider referred to the device data with patients increased from a mean of 2.8 (±1.2) to 6.1 (±3.1) times per observed visit (p=0.0002). A significantly larger proportion of the children looked at the device data with the new application (61% at baseline vs. 94% at study end, p=0.015). HCPs liked the use of color to indicate data variability, the graphical web-based user interface, integration of the data in one application, and the ability to remotely access data via the web for telehealth. They found the application most useful for initiating patient conversations and education. Remaining challenges include the need for automated data upload and integration with electronic medical records. Future studies of HCP use of the application will focus on clinical outcomes and effects on patient engagement and self-management.

941-P

Continuous Glucose Monitoring (CGM) Provides Enhanced Sensitivity Compared with Self-Monitored Blood Glucose (SMBG) for Detecting Hypoglycemia during T2D Clinical Trials

MARCIA A. TESTA, SERGIO SALDIVAR-SALAZAR, MAXWELL SU, JOHANNA F. HAYES, DONALD C. SIMONSON, BOSTON, MA, Wellesley Hills, MA

Documenting hypoglycemia during clinical trials relies primarily on SMBG ≤ 70 mg/dL (3.9 mmol/L) with or without symptoms; however, hypoglycemia unawareness, sleep, and prandial-based sampling might lead to underestimation and lower detection of treatment differences. To quantify sensitivity and detection rates using CGM vs. SMBG, we analyzed hypoglycemia (Hypo: glucose ≤ 70 mg/dL) data from 73,941 SMBG samples collected simultaneously with masked CGM (iPro®2) during four 6-day CGM sessions (10,390 person-days) in 822 T2D patients participating in three 20-26 week trials testing insulin regimens (glargin with/without metformin, lispro, and peglispro (n = 539)) and triple combination therapy (n = 143). For SMBG vs. CGM, total Hypo events were 864 (n = 298 patients) vs. 2,935 (n = 494) at any time of day (daily), and 108 in n = 2,109 (n = 383) nocturnally 12:01-6:00 AM. Poisson regression of Hypo and exposure time, with study regimen, time of day and monitoring method as independent variables, indicated CGM nocturnal Hypo risk (IRR [95% CI]) was higher than CGM daily Hypo risk (1.865 (0.957), 1.559 to 1.791). However, SMBG detected only 29.4% of CGM daily Hypo (0.294 [0.011], 0.273 to 0.318). The interaction term indicated that the SMBG nocturnal detection bias resulted in 70% fewer Hypo events (0.303 [0.033], 0.246 to 0.375) than CGM, thereby detecting only 9.9% of those detected by CGM (0.089 [0.009], 0.073 to 0.106). CGM also detected higher Hypo risk for insulin and metformin compared to triple oral combination therapy (daily = 1.16 [0.085], 1.007 to 1.340, p = 0.04; nocturnal = 1.247 [0.131], 1.015 to 1.531, p = 0.04) when A1C levels were comparable. SMBG did not detect these differences (p = 0.09 and p = 0.94). Using CGM vs. SMBG to detect hypoglycemia can improve comprehensive care and safety benefit assessments during diabetes clinical trials by providing greater sensitivity and representative 24-hour sampling.

942-P

The Effect of Flash Glucose Monitoring on Glycemic Control in Patients with Type 1 Diabetes

GRY H. DØRFLINGER, JAKOB A. ØSTERGAARD, SANNE FISKER, SOREN T. KNUDSEN, TROELS K. HANSEN, Aarhus, Denmark

Introduction: Freestyle Libre Flash glucose monitoring system is a new approach to self-monitoring of glucose. We investigated the effect on gly-
caemic control of applying this system in patients with type 1 diabetes in a real world clinical setting.

Materials and Methods: A total of 210 consecutive patients with type 1 diabetes were included in an observational study investigating the change in glycemic control upon introducing Freestyle Libre Flash Glucose monitoring (FGM) system (Abbott Diabetes Care Ltd, Range Road Winyay, Dxon, OX29 OYL, UK). HbA1c was monitored prior to the application of FGM and every 3-4 months during a follow-up of between 3 and 15 months.

Results: HbA1c decreased significantly by 5 mmol/mol (IQR 10, P < 0.001) after 3 months as compared with baseline, whereafter HbA1c stabilized. When subdividing patients according to baseline glycemic control (HbA1c <53 mmol/mol, 54-70 mmol/mol, >70 mmol/mol) at inclusion in the study, we found a significant decrease in HbA1c in two groups (54-70: 4 mmol/mol, P=0.001, >70: 7 mmol/mol, P<0.001) from baseline to 3 months.

Conclusion: In this observational study, we found a significant decrease in HbA1c levels after the introduction of flash glucose monitoring in subjects with type 1 diabetes; this decrease was maintained throughout the 12-month study period.

Figure.

Effects of Basal Doses of Insulin Treatment in Type 1 Diabetes Evaluated by Continuous Glucose Monitoring on Glycemic Variability

Aims: To characterize the use of Flash Glucose Monitoring (FGM) in type 1 diabetic patients in a pediatric hospital one year after reimbursement by the public health insurance in Belgium.

Methods: This retrospective study included all type 1 diabetic children and adolescents who switched to FGM with specific education in our center and for whom FGM, data, and severe hypoglycemic records were available. Results: Of the 324 subjects (aged 4-20 years) included, 58 (18.1%) refused to use FGM. At baseline, users were younger [median (IQR)] 13.6 (10.9-16.3) vs. 15.2 (12.2-17.5) years; p=0.012 and performed more SMBG tests (4.3 (3.8-5.0) vs. 4.1 (3.5-4.4) per day; p=0.008) than non-users. During follow-up, FGM users increased glucose monitoring from 4.3 (3.8-5.0) to 7.0 (5.0-10.0) time per day (p=0.011) while severe hypoglycemic events decreased from 6.8% to 0.9% (p=0.011). At the end of follow-up (12.7 (11.9-13.5) months), there were less severe hypoglycemic events in FGM users than in non-users (0.9% vs. 8.3%; p=0.026) but no difference in A1c. In multivariate analysis, ΔA1c during follow-up was independently related to A1c at baseline (R=0.419, p<0.001) for FGM users, and negatively with the frequency of glucose scans (R=0.16; p<0.001).

ADA-Supported Research  Moderated Poster Discussion

A Novel, Nonenzymatic Strategy for Stable, Optical Glucose Detection in Small Volumes of Fluid

BING WANG, GUILLERMO BAZAN, SUMITA PENNATHUR, B.N. QUEENAN, KAREN SCIDA, Santa Barbara, CA

The performance of any continuous glucose monitor (CGM) cannot exceed the performance of the underlying glucose sensor. Commercially available CGMs are built around the enzyme glucose oxidase. However, the performance of the enzyme is known to drift over time; accordingly, existing CGMs must be calibrated over periods of hours to days and replaced over periods of weeks. To overcome these fundamental limitations, we have developed a non-enzymatic glucose detection strategy that offers the promise of significantly improved stability and sensitivity. Specifically, we have designed and synthesized a water-soluble, molecular recognition element, which binds glucose with appropriate specificity and selectivity (Kd = 1.9 mM for glucose vs. Kd = 3.3 mM for fructose). The molecular recognition of glucose by our synthetic probes activates interactions between fluorescence-based reporters. Moreover, by coupling the recognition element with a light-harvesting molecular system with high optical cross-section, we are able to amplify optical signals that betray the presence of glucose, making it possible to carry out measurements in volumes as small as picoliters using off-the-shelf LEDs and photodetectors. Our detection platform also offers broad tunability; by altering the molecular recognition element and/or optical reporter we seek to achieve stable, optical detection of other sugars and biomarkers.

Supported By: American Diabetes Association (17-17USN-18 to S.P.)
Characteristics of Children Discontinuing Flash Glucose Monitoring
ANISSA MESSAAOUI, SYLVIE TENOUTASSE, LAURENT CRENIER, Brussels, Belgium

Aims: To study characteristics of type 1 diabetic patients who stop Flash Glucose Monitoring (FGM) during the first year of use in a pediatric hospital.

Methods: This retrospective study included all type 1 diabetic children and adolescents who switched to FGM in our center and for whom A1c, FGM data, sensor related adverse events and satisfaction scores were available.

Results: On the 278 subjects (aged 4-20 years) included in the study, 44 (15.8%) came back to SMBG during the first 12.7 (11.9-13.5) months [median (IQR)] of follow-up. Adverse events were more often reported, including premature loss of the sensor (31.8% vs. 12.4%; p=0.001), skin reactions (18.2% vs. 2.6%; p<0.001) and local pain (6.8% vs. 0%; p<0.001). They were also less satisfied by the FGM than continuing users (p<0.001). Subjects who discontinued FGM had a diabetes of longer duration (7.3 (4.5-10.5) vs. 5.2 (3.1-7.7) years; p=0.002) and a higher A1c (7.9% (7.5-8.4) vs. 7.5 (6.8-8.0); p=0.002). After two months, they scanned less often (6.0 [4.0-7.8] vs. 7.0 [5.0-10.0] per day; p=0.022) and those scanning less than 7 times a day stopped FGM more quickly (p<0.001).

Conclusions: In a pediatric population FGM is discontinued more often in patients experiencing adverse events, with higher A1c and scanning less. These patients are also older and have a diabetes of longer duration.
App from Google Play store for the last 6 months. Meaningful health interactions with health coach were identified in 317 patients which were categorized into medication, diet, exercise, and self-monitoring blood glucose (SMBG). Descriptive statistics was applied to analyze the data, to assess clinical outcomes.

Results: A total of 10800 health interactions were captured, of which 2000 quality interactions were categorized as meaningful interactions. Among these interactions 29% on diet, 21% on exercise, 19% on medication change, 4% on insulin dose, 2% on hypoglycemia and 25% on meaningful use of SMBG data. SMBG was performed >2times/week by 65% of study population. Pre-meal and post-meal SMBG target were achieved in 59% and 24% of patients, respectively. 28% achieved control reductions in <2 weeks and no hypoglycemic episodes occurred in any of the patients. There was a considerable reduction in mean HbA1c (-0.7%), fasting plasma glucose (1-41.5mg/dL) and post-prandial glucose (1-100.7mg/dL) at 3 months follow-up.

Conclusions: The current analysis indicates that patient interactions with health coach through an Apollo Sugar app is a modern improved method of behavioral and clinical care, to achieve long term continuity of care for change in outcome of hard end points.

950-P

Assessing Glucose Trend Accuracy with a Novel Continuous Glucose Monitoring System
TERRI JOHNSON, XIAOHE ZHANG, ANDREW BALO, San Diego, CA

In addition to point accuracy, continuous glucose monitoring (CGM) devices should be evaluated on trend accuracy to determine whether they provide accurate and timely tracking of glucose fluctuations. We evaluated trend accuracy in a study of the investigational G6 Factory-Calibrated System (“G6 FC,” Dexcom), which provides real-time glucose measurements and trend indicators. A total of 76 subjects enrolled (49 children ages 6-17 years and 27 adults) at four U.S. clinical sites. 73 had type 1 diabetes. Participants attended 1 or 2 clinic sessions during which CGM readings were compared to reference venous YSI glucose obtained every 15 minutes. Trend accuracy was assessed using R-deviation, which computes the difference between “instantaneous” rates of glucose change for the CGM and the reference rate of glucose change. Approximately 94% of data had less than ±1 mg/dL/min difference from the reference rate of change (95% for adults vs. 93% for children). When YSI glucose values were falling rapidly (<2 mg/dL/min), the G6 FC showed that glucose values were falling moderately to rapidly 83% of the time; when the glucose values were rising rapidly (>2 mg/dL/min), the G6 FC showed that glucose values were rising moderately to rapidly 91% of the time (Table). Accurate tracking of glucose trends with the novel G6 FC CGM system will provide additional assurance to the patients relying on these devices for diabetes management decisions.

Table. G6 FC System’s Concurrence on Rate of Change.

<table>
<thead>
<tr>
<th>Change Rate of</th>
<th>Matched Pairs N</th>
<th>G6 Rate of Change (mg/dL/min)</th>
<th>G6 FC Rate of Change (mg/dL/min)</th>
<th>&lt; -2</th>
<th>[-2, -1)</th>
<th>[-1, 0)</th>
<th>[0, 1)</th>
<th>[1, 2)</th>
<th>&gt; 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; -2</td>
<td></td>
<td></td>
<td></td>
<td>45.0%</td>
<td>37.5%</td>
<td>11.5%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>40</td>
</tr>
<tr>
<td>[-2, -1)</td>
<td></td>
<td></td>
<td></td>
<td>3.6%</td>
<td>95.5%</td>
<td>0.0%</td>
<td>2.3%</td>
<td>0.4%</td>
<td>0.0%</td>
</tr>
<tr>
<td>[-1, 0)</td>
<td>0.2%</td>
<td></td>
<td></td>
<td>3.4%</td>
<td>5.3%</td>
<td>34.8%</td>
<td>3.6%</td>
<td>0.0%</td>
<td>270</td>
</tr>
<tr>
<td>[0, 1)</td>
<td>0.0%</td>
<td></td>
<td></td>
<td>0.0%</td>
<td>0.0%</td>
<td>1.6%</td>
<td>36.1%</td>
<td>50.2%</td>
<td>11.3%</td>
</tr>
<tr>
<td>[1, 2)</td>
<td>0.0%</td>
<td></td>
<td></td>
<td>0.0%</td>
<td>0.0%</td>
<td>2.4%</td>
<td>6.0%</td>
<td>27.7%</td>
<td>63.3%</td>
</tr>
<tr>
<td>&gt; 2</td>
<td>0.0%</td>
<td></td>
<td></td>
<td>0.0%</td>
<td>0.0%</td>
<td>2.4%</td>
<td>6.0%</td>
<td>27.7%</td>
<td>63.3%</td>
</tr>
</tbody>
</table>

951-P

WITHDRAWN

952-P

Retrospective Flash Glucose Monitoring Analysis in Patients with Type 2 DM, Closer to Target
MANJU S. CHAWLA, PURVI M. CHAWLA, MIKHIL C. KOTHARI, AMBARI F. SHAIKH, NAVNEET WADHWA, Mumbai, India, Delhi, India

Undiagnosed or poorly managed diabetes may be associated with several complications including cardiac ailments, lower limb amputations, blindness or renal disease. Projections state that India would lead this increasing public health concern with a staggering incidence of 134.3 million patients by the year, 2045 based on current trends. We utilized the Freestyle Libre Pro Flash Glucose Monitoring (FGM) system, a novel automated ambulatory glucose profile (AGP) reporting system to identify precise hyperglycemic spikes in a specific patient population. There were 53 T2DM patients with an AGP-estimated HbA1c close to target levels (HbA1c between 7-8%). The 24-hour glycemic patterns were divided into 2-hour time slot patterns for review and analyses; thus, identifying precise spikes contributing to hyperglycemia in patients not achieving their target HbA1c. The highest glycemic peaks were observed between 10 am to 12noonand between 10 pm-12 am (mean interstitial glucose (mg/dL) ± SD of 204 ± 36 and 168 ± 23) coinciding with the post-breakfast and post-dinner periods, respectively. As shown in Table 1, the variation in glycemic spikes ofeach of the 2-hour slots was statistically significant (p<0.0001). FGM helped us identify glycemic variability and specifically, the contribution of post-breakfast hyperglycemia in precluding patients from achieving their target metabolic goals.

Table 1 – Glycemic variability across 2-hour time slots determined by AGP

<table>
<thead>
<tr>
<th>Time slots</th>
<th>Mean ± SD</th>
<th>95% CI</th>
<th>Min, Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 am – 2 am</td>
<td>166 ± 26</td>
<td>159-173</td>
<td>116, 234</td>
</tr>
<tr>
<td>2 am – 4 am</td>
<td>139 ± 25</td>
<td>132-146</td>
<td>90, 199</td>
</tr>
<tr>
<td>4 am – 6 am</td>
<td>125 ± 23</td>
<td>118-131</td>
<td>78, 189</td>
</tr>
<tr>
<td>6 am – 8 am</td>
<td>135 ± 23</td>
<td>128-141</td>
<td>99, 205</td>
</tr>
<tr>
<td>8 am – 10 am</td>
<td>172 ± 36</td>
<td>160-181</td>
<td>103, 267</td>
</tr>
<tr>
<td>10 am – 12 noon</td>
<td>204 ± 36</td>
<td>195-214</td>
<td>118, 308</td>
</tr>
<tr>
<td>12 noon – 2 pm</td>
<td>183 ± 27</td>
<td>176-191</td>
<td>127, 262</td>
</tr>
<tr>
<td>2 pm – 4 pm</td>
<td>172 ± 27</td>
<td>165-180</td>
<td>104, 226</td>
</tr>
<tr>
<td>4 pm – 6 pm</td>
<td>175 ± 29</td>
<td>167-183</td>
<td>92, 235</td>
</tr>
<tr>
<td>6 pm – 8 pm</td>
<td>177 ± 27</td>
<td>170-184</td>
<td>125, 241</td>
</tr>
<tr>
<td>8 pm – 10 pm</td>
<td>181 ± 26</td>
<td>179-188</td>
<td>111, 255</td>
</tr>
<tr>
<td>10 pm – 12 am</td>
<td>186 ± 23</td>
<td>180-193</td>
<td>121, 224</td>
</tr>
</tbody>
</table>

953-P

Real-World Avoidance of Glucose Excursions with the Guardian Connect CGM System’s Predictive Alerts
OHAD COHEN, SINU BESSY ABRAHAM, CHANTAL M. MCMAHON, PRATIK AGRAWAL, ROBERT VIGERSKY, Tolochenaz, Switzerland, Northridge, CA

The Medtronic GuardianTM Connect continuous glucose monitoring (CGM) system, with predictive high and low glucose alerts, allows users to view sensor glucose (SG) data on a smartphone that notifies them 10-60 minutes before an excursion. The rates of alerts and outcomes of users on the GuardianTM Connect system were evaluated. We identified 2,541 users with >5 days of SG data in the CareLinkTM database from Jan 2, 2017-Sep 5, 2017 (data collected Jan 2, 2017-Dec 14, 2017). Excursions were identified when
SG values were beyond the users’ preset SG threshold limit for ≥15 min. As a control, alerts were simulated during user alert-disabled periods to compare excursion frequency. Excursion durations following the alert times were segmented into avoided, ≤20min, 20-60 min, and >60min. Simulated SG limits were 202mg/dL (11.1mmol/L) for high and 70mg/dL (3.9mmol/L) for low. Simulated predictive times before excursions were 12.5min for high and 17.5min for low. The Table shows percentages of each alert resulting in an excursion. Users who enabled predictive alerts avoided 60% of low and 39% of high events. The percentage point improvement for excursions avoided was 28% and 31% following predicted low and high alerts vs. control. Standalone CGM technology, like the Guardian™ Connect system, with predictive alerts are useful for tracking SG and enabling timely actions that help avoid high and low excursions.

### Table.

<table>
<thead>
<tr>
<th>Alert Type</th>
<th>High SG Predictive Alert</th>
<th>Low SG Predictive Alert</th>
<th>High SG Predictive Alert</th>
<th>Low SG Predictive Alert</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Alert Count</td>
<td>21583</td>
<td>39438</td>
<td>27040</td>
<td>35714</td>
</tr>
<tr>
<td>Avoided Excursion Count</td>
<td>85184</td>
<td>23194</td>
<td>22840</td>
<td>17451</td>
</tr>
<tr>
<td>% of total alerts</td>
<td>39%</td>
<td>60%</td>
<td>8%</td>
<td>32%</td>
</tr>
<tr>
<td>≤ 20 min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excursion Count</td>
<td>25790</td>
<td>64065</td>
<td>28041</td>
<td>7646</td>
</tr>
<tr>
<td>% of total alerts</td>
<td>11%</td>
<td>16%</td>
<td>11%</td>
<td>22%</td>
</tr>
<tr>
<td>20-60 min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excursion Count</td>
<td>36792</td>
<td>63755</td>
<td>44398</td>
<td>7498</td>
</tr>
<tr>
<td>% of total alerts</td>
<td>17%</td>
<td>17%</td>
<td>18%</td>
<td>23%</td>
</tr>
<tr>
<td>&gt; 60 min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excursion Count</td>
<td>72158</td>
<td>27156</td>
<td>175521</td>
<td>8719</td>
</tr>
<tr>
<td>% of total alerts</td>
<td>33%</td>
<td>7%</td>
<td>69%</td>
<td>25%</td>
</tr>
</tbody>
</table>

### Safety of Microdose Dexamethasone Acetate in the Eversense® Long-Term Implantable Continuous Glucose Monitoring System

**E.L. KELLEY, HARITHA HARIDAS, CARRIE LORENZ, Germantown, MD**

**Background:** Dexamethasone (DEX) is used in a variety of implantable medical devices to decrease inflammation and improve outcomes. The implantable Eversense® CGM System (Senseonics, Inc.) includes a silicone collar which slowly releases DEX acetate throughout the lifetime of the sensor. Studies were performed to characterize the potential user risk to dexamethasone acetate exposure.

**Methods:** Clinical trial subjects underwent frequent blood sampling for analysis of plasma DEX levels. Chemical testing of 90-day sensor explants was used to measure residual DEX content. Finally, a post market clinical follow-up study (PMCF) is currently ongoing which monitors the rate of serious device-related, procedure-related, or drug (DEX) related adverse events through approximately 24 months.

**Results:** In two trials (N=161, 86 with 2 sensors, 75 with 1 sensor), blood tests were performed to the 2 ng/mL level with no detectable plasma DEX. In a third trial (N=39), the limit of detection was reduced to 0.050 ng/mL. Blood samples from 8 patients inserted with one sensor had no measurable DEX plasma levels. Among 27 patients inserted with two sensors, the highest level of DEX detected was 0.114 ng/mL on day 2 post-insertion. All samples were below the detectable limit by day 8. Literature review states at plasma levels < 1 ng/mL no systemic effect occurs. Testing of sensor explants determined that 0.3 mg of DEX is eluted over 90 days. No adverse events related to exposure to DEX have been reported to date in the PMCF.

**Conclusions:** Dexamethasone acetate, which was selected to reduce the inflammatory response of the implantable sensor, was found to be safe. Plasma DEX levels after extended use are well below the concentration necessary for a pharmacological response, demonstrating safety of the Eversense Sensor with regard to clinical adverse effects attributable to chronic DEX exposure and that this risk should not grow over time.
Regular blood glucose self-testing is considered to be the most painful procedure during daily treatment routine for patients with diabetes mellitus. This pilot study was undertaken to evaluate the performance of TensorTip CoG, a non-invasive glucose monitoring device (NI-CoG, CNOGA Medical, Israel) on glycemic control and daily measurement aspects in patients with type 1 and type 2 diabetes.

The study was performed with 6 type 1 patients (T1D: 3 male/3 female, age: 43±16 years, HbA1c: 8.0±0.5%), and 15 type 2 patients (T2D: 8 male/7 female, 62±6 years, 7.2±1.3%). The participants used the Ni-CoG device at home after an initial standardized meal experiment to evaluate device performance in comparison to a standard reference method (YSI Stat2300 plus). In addition, HbA1c was assessed and a treatment satisfaction questionnaire was completed after a period of three months of home use.

During the meal experiment, Ni-CoG showed good accuracy (mean bias: 15.3%, consensus error grid: 100% in zones A and B). A trend for HbA1c improvement was seen in both groups over 3 months (T1D: -0.22%, T2D: -0.1%, n.s.). Patients reported to measure more frequently, and to feel more comfortable with the non-invasive measurement procedure. Use of the device in the study initiated the general desire to switch to the new device for daily routine use.

The non-invasive TensorTip device was shown to increase the frequency of glucose testing and to have a positive impact on patients’ perception of the measurement procedure. There was also an initial trend for improvements of glycemic control within the first three months of use in this pilot study.

Supported By: CnoGa Medical Ltd.

**Impact of a Noninvasive Blood Glucose Device on Glycemic Control and Daily Routine Measurement Aspects—Results of a Pilot Study**

**ANDREAS PFÜTZNER, ALEXANDER LIER, SANJA RAMLJAK, FILIZ DEMIRCİK, Mainz, Germany**

**957-P**

**Beneficial Effect of Flash Glucose Monitoring Persists in a Two-Year Perspective—A Clinical Follow-Up Study of 334 Individuals with Type 1 Diabetes**

**MAGNUS LONDAHL, KATARINA FAGHER, PER KATZMAN, KARIN FLIPSSON, Lund, Sweden**

Short term follow-up studies indicate that use of Flash glucose monitoring (FGM) improves metabolic control in people with type 1 diabetes. Whether this effect persists is unknown.

The aim of this study was to evaluate long-term effects on HbA1c and treatment satisfaction in people with type 1 diabetes after introduction of FGM in a university hospital diabetes clinic. Treatment satisfaction was measured using DTSQs questionnaires at the one year follow-up. Of the first 334 patients who were introduced to FGM 80.5% were still users after 2 years, 8.7% changed to a CGM-system, 6.6% stopped due to skin reactions, 3.4% did not want to continue and 1.3% had died. Baseline HbA1c among continuers was 71.8±16.6 mmol/mol (8.7%). Compared to baseline, HbA1c was -0.5±0.8 mmol/mol after 1 year and 9.0±11.8 mmol/mol lower after 2 years. Self-estimated treatment satisfaction after 1 year was 2.4±0.7 (±3 to -3) and rating for continued FGM use was 2.87±0.33. Unacceptable high blood glucose was less often present (-0.6) as were unacceptable low blood glucose levels (-0.3).

Conclusions: Use of FGM adds clinical significant advantage to individuals with 1 diabetes in terms of HbA1c reduction and improved self-estimated treatment satisfaction also in a 2-year perspective.

Supported By: Lund University, Crafoord Foundation

**958-P**

**Use of Real Time Continuous Glucose Monitoring (CGM) in Real Life Clinical Practice Compared with Finger-Stick Glucose Monitoring**

**ELENA TOSCHI, CHRISTINÉ SYNE, ASTRID ATAKOV-CASTILLO, JORDAN GREENBERG, TORI GREEVES, SAM P. CARL, MEDHA MUNSHI, Boston, MA**

Background: Studies have shown benefits of CGM in management of type 1 diabetes (T1D), however, it is not yet clear if the benefits are maintained in a real-life clinical practice.

Methods: We evaluated 2 groups of adults (age 18-35 years) with T1D: One using CGM and the other using glucometer. Patients underwent either 2-week blinded CGM or assessment from personal CGM over 2 weeks. Patients also completed questionnaires for demographics, surveys for fear of hypoglycemia (HSF II), hypoglycemic unawareness, and problem areas in diabetes Questionnaire (PAID)). Glycemic control was measured by A1c.

Results: We evaluated 33 patients with T1D (15 using CGM and 18 using glucometer); average age 27 years, duration of diabetes 10 years, education 7 years. CGM users had better glycemic control as seen by A1c of 7.5% vs. 8.5 (p<0.05). 40% of patients using CGM had clinically significant hypoglycemia (glucoses<54 for >15 mins/episode) compared to 66% in glucometer-users (mean duration 18 min/day vs. 27 min/day) (p<ns). CGM users spent longer time in range (70-180 mg/dl) compared to glucometer-users (14 hours/day vs. 12 hours/day). Hypoglycemia unawareness was reported by 44% of CGM users compared to 14% of glucometer-users. More CGM-users reported checking SMBG >6 times per day, and worried more regarding nocturnal hypoglycemia (81% vs. 57%). Diabetes-related distress was lower in RT-CGM users (PAID score 27 vs. 34).

Conclusion: In a clinical setting, despite more hypoglycemic unawareness and more worry regarding hypoglycemia, T1D patients who used RT-CGM had better glycemic control, higher time spent in range, and lower risk of hypoglycemia compared to glucometer-users.

**959-P**

**Real-World Data from the MiniMed™ 670G System Commercial Launch**

**PRATIK AGRAWAL, MICHAEL STONE, SHWETA GOPALAKRISHNAN, CATHERINE FOGEL, SCOTT W. LEE, FRANCINE R. KAUFMAN, Northridge, CA**

The Medtronic MiniMed™ 670G hybrid closed-loop system with SmartGuard™ technology, which automatically adjusts basal insulin delivery, was released for commercial use in the U.S. in March 2017. Data from the first 13,906 patients to use the system are reported.

MiniMed™ 670G data from patients who voluntarily uploaded to CareLink™ Personal software, from 3/17/17 to 12/14/17, were de-identified and
analyzed if there were ≥7 days of sensor wear. Comparisons of glycemic metrics between 258,415 patient-days in the initial open-loop Manual Mode and 724,220 patient-days after starting closed-loop Auto Mode were made. Data were compared for patients 7-13 years, 14-21 years, 22-60 years, and ≥60 years.

The Table shows glycemic metrics, including time in target range (TIR, 70-180 mg/dL), during Manual Mode and after Auto Mode start for all users and by age group. Children and teens had lower baseline TIR and more hyperglycemia in Manual Mode vs. adults, but a similar magnitude of improvement when in Auto Mode. Older adults had the most optimal glycemic with Auto Mode. TIR was higher in patients with greater time in Auto Mode. For those in Auto Mode 50-59% of the time, mean TIR was 65%; for Auto Mode 60-80% of the time, TIR was 68%; and for Auto Mode >80% of the time, TIR was 74%.

Overall, data from the commercial launch of the MiniMed™ 670G system mirrored the pivotal trial results for all ages and showed an increase in TIR with less hypoglycemia and hyperglycemia.

<table>
<thead>
<tr>
<th>Table.</th>
<th>Glycemic Outcomes (Mean±SD) 48-Hour AP</th>
<th>SAP Run-In Week</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage Time 70-180, mg/dL</td>
<td>88.0±7.7</td>
<td>74.6±9.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percentage Time 80-140, mg/dL</td>
<td>60.1±13.4</td>
<td>45.2±10.3</td>
<td>0.004</td>
</tr>
<tr>
<td>Percentage Time &lt;70, mg/dL</td>
<td>1.5±1.8</td>
<td>7.8±5.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percentage Time &gt;180, mg/dL</td>
<td>10.5±7.7</td>
<td>17.6±10.4</td>
<td>0.081</td>
</tr>
<tr>
<td>Mean CGM, mg/dL</td>
<td>130.1±14.7</td>
<td>135.1±18.8</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>Standard Deviation, mg/dL</td>
<td>32.9±6.1</td>
<td>50.3±10.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of daily hypoglycemic events (CGM &lt;70 mg/dL for ≥15 minutes)</td>
<td>0.6±0.6</td>
<td>1.7±0.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Supported by: JDRF (1-SRA-2016-147-M-R), Insulet Corporation, Dexcom, Inc.

**Clinical Diabetes/Therapeutics**

**Poster 962-P**

**WITHDRAWN**

**Poster 963-P**

**The MiniMed™ 670G Hybrid Closed-Loop (HCL) System and Patient-Reported Outcomes Concerning Quality of Life Measures**

SHWETA GOPALAKRISHNAN, CATHERINE FOGEL, JOHN MUECKLER, Northridge, CA

Patient-reported outcomes are important in assessing the impact of new diabetes therapies on patient perceptions of quality of life (QoL). The QoL of patients using the Medtronic MiniMed™ 670G HCL system with SmartGuard™ technology, released for commercial use in March 2017, was examined. MiniMed™ 670G HCL system users (n=198) completed the validated Diabetes-39 (D-39) questionnaire prior to starting HCL system therapy and at 3-4 months post start. QoL was evaluated on a 7-point scale (1=Not Affected at All to 7=Extremely Affected) across 5 categories: energy and mobility, diabetes control, anxiety and worry, social burden, and sexual functioning. Paired t-test was used to compare the mean score for each attribute, and a two-tailed t-test determined statistical significance from baseline to 3-4 months after MiniMed™ 670G system use. All patients had responses indicating a positive experience after use of the system in Auto Mode. For all 5 categories, 160/198 patients (81%) experienced an outcome in the positive direction. The Table shows the top 10 criteria in which statistically significant improvement was observed. In addition to the previously reported improvements in glycemic control, these findings suggest that the MiniMed™ 670G system improves multiple domains in self-reported QoL measures, and particularly those concerning adherence to diabetes management.
Clinical Therapeutics/New Technology—Insulin Delivery Systems

Open Artificial Pancreas System Reduced Hypoglycemia and Improved Glycemic Control in Patients with Type 1 Diabetes


This study sought to develop and implement a usability/preference survey to compare the pen devices used with innovator insulin glargine and MK-1293 (Pen X) in Type 1 and 2 diabetes patients and certified diabetes educators (CDEs) in the US, Canada, and the UK were recruited from commercial panels. Several rounds of qualitative research with both groups were conducted to develop and refine the survey. Respondents were asked to perform two mock injections (into a cushion pad) for each of the two insulin pens. Order was randomized and after each set of injections, respondents completed the survey. Non-inferiority analyses were conducted to compare ratings of the pens as the primary analysis; two-tailed tests were also conducted. 296 respondents completed the study (177 patients and 119 CDEs). The mean age was 53.2 years for patients and 49.4 years for CDEs; 55.9% and 1.7% were male, respectively; 27.1% of patients were type 1 and 51.2% were type 2. Both patients (66.7%) and CDEs (58.0%) preferred Pen X overall. Individual ratings are reported in Table. The qualitative research results indicated our measure had appropriate content validity for assessing pen preferences. The main results suggested that the appearance and function of Pen X is non-inferior to the insulin glargine pen from the perspective of both patients and CDEs and, in many cases, superior.

Table.

<table>
<thead>
<tr>
<th>Patients (N=177)</th>
<th>CDEs (N=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rated insulin glargine pen higher</td>
<td>Rated both pens identically</td>
</tr>
<tr>
<td>8.8%</td>
<td>70.1%</td>
</tr>
<tr>
<td>6.8%</td>
<td>71.4%</td>
</tr>
<tr>
<td>4.5%</td>
<td>74.6%</td>
</tr>
<tr>
<td>8.5%</td>
<td>57.6%</td>
</tr>
<tr>
<td>13.6%</td>
<td>57.6%</td>
</tr>
<tr>
<td>4.0%</td>
<td>34.5%</td>
</tr>
<tr>
<td>21.5%</td>
<td>11.9%</td>
</tr>
</tbody>
</table>


Clinical Diabetes/Therapeutics

Preference Differences between Insulin Glargine and MK-1293 Pens among Patients with Diabetes and Certified Diabetes Educators

By BERHANU ALEMAYEHU, MARCO DIBONAVENTURA, ALLISON M. NGUYEN, MICHAEL CRUTCHLOW, Koniwot, NJ, New York, NY, North Wales, PA, Upper Gwynedd, PA

This study sought to develop and implement a usability/preference survey to compare the pen devices used with innovator insulin glargine and MK-1293 (Pen X). One type and 2 diabetes patients and certified diabetes educators (CDEs) in the US, Canada, and the UK were recruited from commercial panels. Several rounds of qualitative research with both groups were conducted to develop and refine the survey. Respondents were asked to perform two mock injections (into a cushion pad) for each of the two insulin pens. Order was randomized and after each set of injections, respondents completed the survey. Non-inferiority analyses were conducted to compare ratings of the pens as the primary analysis; two-tailed tests were also conducted. 296 respondents completed the study (177 patients and 119 CDEs). The mean age was 53.2 years for patients and 49.4 years for CDEs; 55.9% and 1.7% were male, respectively; 27.1% of patients were type 1 and 72.9% were type 2. Both patients (66.7%) and CDEs (58.0%) preferred Pen X overall. Individual ratings are reported in Table. The qualitative research results indicated our measure had appropriate content validity for assessing pen preferences. The main results suggested that the appearance and function of Pen X is non-inferior to the insulin glargine pen from the perspective of both patients and CDEs and, in many cases, superior.

Table.

<table>
<thead>
<tr>
<th>Patients (N=177)</th>
<th>CDEs (N=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rated insulin glargine pen higher</td>
<td>Rated both pens identically</td>
</tr>
<tr>
<td>8.8%</td>
<td>70.1%</td>
</tr>
<tr>
<td>6.8%</td>
<td>71.4%</td>
</tr>
<tr>
<td>4.5%</td>
<td>74.6%</td>
</tr>
<tr>
<td>8.5%</td>
<td>57.6%</td>
</tr>
<tr>
<td>13.6%</td>
<td>57.6%</td>
</tr>
<tr>
<td>4.0%</td>
<td>34.5%</td>
</tr>
<tr>
<td>21.5%</td>
<td>11.9%</td>
</tr>
</tbody>
</table>

1. *p<0.05 in non-inferiority and superiority analysis; †p<0.05 only in non-inferiority analysis.
Patient Reported Outcomes (PRO) in a Study of Human Regular U-500 Insulin (U-500R) Delivered by Continuous Subcutaneous Insulin Infusion (CSI) or Multiple Daily Injections (MDI) in Patients with T2D

XIAOMEI PENG, JIEJUN G. CHEN, LUDI FAN, LIZA ILAG, TRANG T. LY, JENNAL JOHNSON, INDIANAPOLIS, IN, Bilkensa, MA

Persons with T2D treated with U-500R have shown improved glycemic control. This prospective analysis evaluated the impact on PRO of U-500R delivered by CSI (using an investigational U-500RD Insulin Management System) or MDI (using a U-100 syringe). This 26-week (week), open-label, parallel trial, 420 patients treated with >200 units/day of insulin for T2D were randomized to CSI (n=209) or MDI (n=211) treatment groups. The Treatment-Related Impact Measure for Diabetes (TRIM-D) and Diabetes Device (TRIM-DD) questionnaires were assessed at baseline, week 14, and week 26. Results are shown in Table 1. TRIM-D scores (overall score and all 5 domain scores) and TRIM-DD overall score in both groups improved significantly from baseline to week 26 (p<0.05). At week 26, change in baseline score for the CSI group was significantly higher than the MDI group in all TRIM-D measures (p<0.05). At week 26, there were no significant differences in the change from baseline score between the CSI and MDI groups in TRIM-DD overall or its domains.

In summary, the U-500R CSI device scored significantly better than MDI in the perceived impact on diabetes treatment (TRIM-D) but not for diabetes device (TRIM-DD). PROs for diabetes treatment improved significantly from baseline to week 26 in patients treated with U-500R by either CSI or MDI.

### Table 1. Patient reported outcomes for U-500R delivered by CSI or MDI in patients with T2D

<table>
<thead>
<tr>
<th>Source (%)</th>
<th>U-500R CSI</th>
<th>U-500R MDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall score</td>
<td>78.0 (78.0)</td>
<td>78.0 (78.0)</td>
</tr>
<tr>
<td>Treatment burden</td>
<td>78.0 (78.0)</td>
<td>78.0 (78.0)</td>
</tr>
<tr>
<td>Daily life</td>
<td>78.0 (78.0)</td>
<td>78.0 (78.0)</td>
</tr>
<tr>
<td>Diabetes management</td>
<td>78.0 (78.0)</td>
<td>78.0 (78.0)</td>
</tr>
<tr>
<td>Compliance</td>
<td>78.0 (78.0)</td>
<td>78.0 (78.0)</td>
</tr>
<tr>
<td>Patients with compliance</td>
<td>78.0 (78.0)</td>
<td>78.0 (78.0)</td>
</tr>
<tr>
<td>Psychological health</td>
<td>78.0 (78.0)</td>
<td>78.0 (78.0)</td>
</tr>
</tbody>
</table>

**WITHDRAWN**
Methods: Data from a recent clinical trial with 12 patients are used for evaluating the ABC method. CIR and ISF values are identified using the ABC method based on the first 6 days of the data, whereas the 7th day is used for the evaluation. The effect of the estimated CIRs and ISFs on the glycemic outcomes is simulated using a deviation based method. The simulation outcomes are compared to the outcomes obtained with the clinically used settings (in the Figure below abbreviated as CUS) that the patients employed on the previous 6 days for calculating their bolus insulin needs.

Results: The CIRs and ISFs estimated by the ABC approach lead in average to a 6.8% reduction in time for hypoglycemia (BG<70 mg/dl) as compared to the clinically used CIR/ISF settings (avg. time in hyperglycemia: from 9.8% to 3.0%, p<0.01). Time in hyperglycemia (BG>180 mg/dl) on the other hand increases only slightly (avg. time in hyperglycemia: 10.9% vs. 9.3%, p=0.08).

Figure:

971-P
Basal Rate Delivery of Different Insulin Pumps—An Accuracy Evaluation
GUIDO FRECKMANN, ULRIKE KAMECKE, DELIA WALDENMAIER, CORNELIA HAUG, RALPH ZIEGLER, Ulm, Germany, Münster, Germany
Continuous subcutaneous insulin infusion is a common therapy for patients with type 1 diabetes, involving the continuous delivery of fast-acting insulin according to preset basal rates. The standard EN 60601-2-24 describes test settings and procedures for the evaluation of infusion pumps in general; however, no acceptance criteria relating to insulin delivery accuracy are stipulated. Most manufacturers specify a basal rate accuracy of ±5%, at least for larger basal rates.

In this study, the accuracy of different insulin pumps was evaluated in an experimental setting based on EN 60601-2-24. The insulin pumps Accu-Chek® Insight, Accu-Chek® Spirit Combo, Animas® Vibe®, MiniMed® 640G, Paradigm® Veo® and mylife® Omnipod® were tested with different infusion sets (IIS). Evaluations were based on the determination of weight increase of water-filled, oil-covered beakers placed on balances into which insulin was delivered by the pumps. Pumps were installed outside of the balance with the infusion set or a steel pipe (for the patch pump), respectively, connected to the beaker. After priming, a basal rate of 0.1 U/h was run for 72 h while weight increases were recorded. Each combination of insulin pump and IIS was tested for 9 times. The total delivery as well as the mean delivery over 1-h windows was calculated.

The total weight increase for all pumps was slightly higher than expected for the programmed basal rate (+0.3% to +2.1%), but within the range specified by the manufacturers. During the first 24 h, larger deviations between the measured and expected delivery were recorded. For 8 of 10 systems, more than 95% of 1-h windows were within ±15% of the weight increase expected with the preset basal rate.

Using a basal rate of 1.0 U/h, all tested systems showed minor deviations when analyzing a period of 72 h; however, stability during the run time, i.e., variation from hour to hour, differed considerably between the tested systems. This might be important with regard to the clinical use of insulin pumps.

Supported By: Roche Diabetes Care

972-P
Delivery of Low Basal Rates in Different Insulin Pumps—An Accuracy Evaluation
RALPH ZIEGLER, ULRIKE KAMECKE, DELIA WALDENMAIER, CORNELIA HAUG, GUIDO FRECKMANN, Münster, Germany, Ulm, Germany
Insulin pumps are commonly used in the therapy of children with type 1 diabetes, among other reasons due to the flexible continuous delivery of low basal rates. The standard EN 60601-2-24 describes test settings and procedures for the evaluation of infusion pumps in general; however, no acceptance criteria related to insulin delivery accuracy are stipulated. Most manufacturers’ specifications are limited to the accuracy of basal rates ≥1 U/h, while far lower basal rates are common in children.

In this study, the accuracy of a 0.1 U/h basal rate delivery of different insulin pumps was evaluated in an experimental setting based on EN 60601-2-24. The insulin pumps Accu-Chek® Insight, Accu-Chek® Spirit Combo, Animas® Vibe®, MiniMed® 640G, Paradigm® Veo® and mylife® Omnipod® were tested with different infusion sets (IIS). Measurements were based on the determination of weight increase of water-filled, oil-covered beakers placed on balances into which insulin was delivered by the pumps. Pumps were installed outside of the balance with the infusion set or a steel pipe (for the patch pump), respectively, connected to the beaker. After priming, a basal rate of 0.1 U/h was run for 72 h while weight increases were recorded. Each combination of insulin pump and IIS was tested for 9 times. The total and the mean delivery over 1-h windows were calculated.

Large differences in total delivery were observed between the tested systems (+4.1% to +24.4% of the expected). During the first 24 h, all deviations were >10% from the expected rate. Evaluation of 1-h windows showed that 31% to 85% of results were within ±15% of the weight increase expected with the set basal rate and large variations between the individual 1-h windows.

With the low basal rate tested in this study, delivery rates calculated from weight increases showed marked deviations from what was expected for this rate. When using insulin pumps in children with low insulin demands, it has to be considered that the basal rate might not be delivered as accurate and as consistent as expected.

Supported By: Roche Diabetes Care

973-P
Looking Beyond HbA1c—Evaluating Glycaemic Control during Closed-Loop Use in Type 1 Diabetes
HOOD THABIT, LALANThA LEELARATHNA, MALGRZATA E. WILINSKA, CARSTEN BENSECH, SABINE ARNOLDS, JULIa K. MAIDER, THOMAS R. PIEBER, MARK EVANS, ROMAN HOVOIRKA, Manchester, United Kingdom, Cambridge, United Kingdom, Neuss, Germany, Graz, Austria
Despite being an established marker of glucose control, HbA1c does not provide insight into hypoglycemia and glycemic variability. As such, HbA1c does not capture these vital attributes of particular interest during closed-loop insulin delivery (CL). We developed a novel index using continuous glucose monitoring (CGM) data, named composite glucose index (COGI), which evaluates CL performance based on 3 key aspects: time in range 70-180 mg/dl, hypoglycemia <70 mg/dl and glucose variability, each contributing up to 50, 35 and 15 points to the composite index respectively. COGI ranges from 0 (worst control) to 100 (best control). We used COGI to assess glucose control in a published, randomised, 3 months day-and-night hybrid CL study in type 1 diabetes adults (n=32, baseline A1c 7.6% [60 mmol/mol], diabete
tes duration 21 years), compared to sensor augmented pump therapy. We hypothesized that COGI may show benefits of CL even in the absence/limited HbA1c improvement. For the whole cohort, HbA1c difference was -0.3±0.6% (P=0.002) in favour of CL, and COGI improved by +10 (p<0.005, 95% CI 7 to 11). In those without HbA1c improvement (n=15) notably, overall COGI and individual components improved with CL use (Table), mainly attributable to the hypoglycemia component of COGI. We demonstrate the wider benefits of CL using a novel composite CGM index. COGI may have a role in evaluating glycemic control during CL use, beyond HbA1c.

Table. HbA1c and Composite Glucose Index (COGI) in Those Without HbA1c Improvement

<table>
<thead>
<tr>
<th>HbA1c (%) end of treatment arm</th>
<th>7.0±0.9</th>
<th>6.8±1.0</th>
<th>0.056</th>
</tr>
</thead>
<tbody>
<tr>
<td>COGI (out of 100 points)</td>
<td>71±6</td>
<td>60±10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time in range component (out of 50 points)</td>
<td>38±5</td>
<td>33±5</td>
<td>0.003</td>
</tr>
<tr>
<td>Hypoglycemia component (out of 35 points)</td>
<td>26±4</td>
<td>19±9</td>
<td>0.001</td>
</tr>
<tr>
<td>Glycemic variability component (out of 15 points)</td>
<td>9±2</td>
<td>8±2</td>
<td>0.029</td>
</tr>
</tbody>
</table>

Supported By: University of Manchester; JDRF; UK National Institute for Health Research; Cambridge Biomedical Research Centre; UK Wellcome Trust (100574/Z/12/Z); AP@Home Consortium; European Union Seventh Framework Program (ICT FP-240738)
Effect of Medicare (CMS) Insulin Pump Policies in T1D

NICHOLAS B. ARGENTO, JINGWEN LIU, AILEEN HICKEY, ELDGA GAUTSCHI, ALICIAH. McALULIE-FOGARTY, Columbia, MD, Boston, MA

CMS has numerous requirements for insulin pump coverage and obtaining disposable supplies. T1D Exchange surveyed 214 adult T1D patients who had been on a pump with CMS coverage for at least 6 mo on their experience. Median age 67, 64% women, 93% white, 16% on disability, median T1D duration 42 y, median pump use 15 y, mean A1C 7.0%, 82% on pump before starting CMS, 95% current pump users. Of those starting a pump while on CMS, 50% reported challenges, most commonly cost of the supplies (29%) or the pump (24%). Issues with obtaining supplies reported in 57.5%, the most common problems were delays releasing supplies (29%), difficulty getting paperwork completed (23.5%), and seeing an HCP face to face every 90 days (18%). When asked if they had changed pump behaviors because of possible or actual supply delays, 38% answered yes. Most common responses: leaving site in place >3 days (45%), specifically reduce cost (33%), reused pump supplies (34%), used injections to supplement pump (29%), or temporarily stopped pump (17%). Responses to a question about any adverse effects of these actions are shown in Table.

On their experience with CMS compared to prior insurance, a minority thought it was somewhat (4%) or much (6%) better; 31% about the same; 28% found it somewhat worse, and 31% found it much worse.

Conclusion: current CMS pump policies cause increased adverse pump behaviors and outcomes in T1D, and CMS is perceived negatively compared to prior insurers by 59% of respondents.

Table. Adverse Outcomes from Changes in Pump Related Actions, n=88.

<table>
<thead>
<tr>
<th>Question</th>
<th>frequency</th>
<th>percent</th>
<th>Question</th>
<th>frequency</th>
<th>percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>21</td>
<td>22.8</td>
<td>Hospitalization</td>
<td>9</td>
<td>6.5</td>
</tr>
<tr>
<td>Higher blood sugar</td>
<td>37</td>
<td>40.2</td>
<td>More hypoglycemia</td>
<td>15</td>
<td>16.3</td>
</tr>
<tr>
<td>Infection at site</td>
<td>13</td>
<td>14.1</td>
<td>Increased anxiety or frustration</td>
<td>39</td>
<td>42.4</td>
</tr>
<tr>
<td>Pain or irritation</td>
<td>30</td>
<td>34.1</td>
<td>Required emergency pump supply shipment</td>
<td>17</td>
<td>18.5</td>
</tr>
<tr>
<td>More scarring</td>
<td>25</td>
<td>27.2</td>
<td>Needed emergency supplies from local source</td>
<td>13</td>
<td>14.1</td>
</tr>
<tr>
<td>More erratic blood sugar</td>
<td>42</td>
<td>47.7</td>
<td>Other</td>
<td>1</td>
<td>1.1</td>
</tr>
</tbody>
</table>

CSII Use in hospitalized Patients—Adherence to Policy and Safety of Use

KATHERINE YANG, MOHAMMAD B. ATEYA, ROMA GIANCHANDANI, Ann Arbor, MI

Continuous subcutaneous insulin infusion (CSI) therapy is routinely used in diabetes management for patients expecting to use their insulin pumps during hospitalizations. For hospital personnel, this is unfamiliar and complex technology, which necessitates implementing policies and guidelines for standardizing CSII use in the inpatient setting. This study aims to examine adherence to an institutional CSII policy and safety glucoregulators for hospitalized patients using CSII. We performed an IRB-exempt retrospective review of CSII user records from January to June 2017. Policy adherence was evaluated for appropriate provider and nurse order set use and documentation in the electronic medical record. 81 patients with 111 admissions on CSII were evaluated. Mean age was 42±16.9 y, 62% were female and 82% had type 1 diabetes. Median LOS was 5 days for 788 total patient days, HgbA1C 8.3±1.78, and baseline admission blood glucose (BG) was 175 mg/dL. CSII was continued in 62% of admissions with 12.6% discontinuing use due to medical and surgical contraindications. Overall adherence to the policy was high with documented endocrinology consultations in 100%, provider specified basal rates in 96%, specified bolus doses in 92%, specified correction doses in 83%, specified target BG in 90%, and nurse documented verified doses on the MAR in 93%. Nurse documentation of CSII in the Lines/Drains/ Airways flowsheets was 15%, Hypoglycemia (BG<70mg/dL), severe hypoglycemia (BG<40 mg/dL), and uncontrolled hyperglycemia (BG>299mg/dL) were present in 10%, 0.8%, and 10.5% of patient days, respectively. Rates of DKA in CSII users was 0.9%. Policy adherence was effectively achieved for CSII use in hospitals. Rates of hypoglycemia and uncontrolled hyperglycemia were high with very low incidence of severe hypoglycemia or DKA episodes. These results suggest that CSII is possible to safely continue in hospitalized patients, but future studies are necessary to determine how to modify pump rates and optimize glycemic control.

Glucose-Responsive Insulin Delivery with Fast Response Using Charge-Switchable Polymeric Depot

ZHENGU, Alphabet, NC

The conventional method for controlling blood glucose levels (BGLs) involves the repeated subcutaneous injection of insulin, which is challenging to achieve satisfied blood glucose regulation and could often lead to hyperglycemia. Therefore, the development of self-regulated, glucose-triggered insulin delivery systems has attracted considerable attentions these years. In this study, we describe a new glucose-responsive insulin delivery formulation with ultrafast response both in vitro and in vivo, dependent on a glucose-triggered charge switch of a cationic polymer. A designates as polyEDAC<sub>0.4</sub>−FPBA<sub>0.6</sub> with pendant amine and 4-carboxy-3-fluorophenylboronic acid was synthesized. Next, a stable complex with high insulin loading capacity (50%) and slow basal insulin release rate was prepared from an equal weight of insulin and polymer in PBS at 7.4. The addition of F-insulin to glucose solution led to decrease of the glucose level by 10 and 30 mg/dL for 100 and 400 mg/dL glucose solution, respectively, within 10 min. Meanwhile, the Z-potential of polyEDAC<sub>0.4</sub>−FPBA<sub>0.6</sub> nanoparticles was decreased from the original +40 mV in the absence of glucose, to +22 mV in 100 mg/dL glucose solution, and further decreased to less than +8 mV in 400 mg/dL glucose solution. As a consequence, the insulin release kinetic from the complexes was highly glucose dependent. The in vivo therapeutic efficacy of F-insulin was evaluated in type 1 diabetic mouse model induced by streptozotocin. The BGLs of F-insulin treated group decreased to below 200 mg/dL within 30 min, and further maintained BGLs within the normal range (<200 mg/dL) for more than 8 hours.

Supported By: American Diabetes Association/Pathway to Stop Diabetes (1-15-ACE-27)

Real-World Use of Hybrid Closed-Loop Therapy in Pediatric Patients with Type 1 Diabetes

CARI BERGET, LAUREN H. MESSER, LAURA PYLE, EMILY WESTFALL, GREGORY P. FORLENZA, KIMBERLY A. DRISCOLL, Aurora, CO

Objective: To describe the real world impact of the 670G Hybrid Closed Loop (HCL) system on glucose control in pediatric patients with type 1 diabetes (T1D).

Methods: Patients starting the 670G were recruited to participate in a 12-month observational study. Data on 670G use and glycemic outcomes were obtained from pump downloads and chart review as part of routine clinical care. Descriptive statistics are reported as medians (25th%ile, 75th%ile).

Results: Nineteen pediatric patients (14 y (11.7, 17.4); 53% F) with 32 days (26, 44) of 670G data were included. T1D duration was 7 years (3, 9) and HgbAC was 8.5% (7.9, 9.6). Patients spent 70% (35, 85) of each week in HCL. System exits from HCL mode (auto mode) to standard pump mode (manual mode) occurred 0.64 times/day (0.5, 1.05), primarily due to hyperglycemia. Sensor glucose time in target range (70-180 mg/dl) was 60% (50, 64) with 1% of sensor glucose values ≤70 mg/dL. Increased time spent in HCL was correlated with reduced mean sensor glucose and standard deviation of glucose, and increased time in target range (Table).

Conclusions: Youth using the 670G in clinical care were able to stay in HCL most of the time in the initial weeks of system use. HCL use may improve glucose control for pediatric patients with T1D. Data collection is ongoing and will elucidate the impact of the 670G on glycemic control longitudinally and describe patient use of the system in real-world conditions.

Table. Correlation of % Time in HCL ‘Auto Mode’ with Glucose Variables.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Spearman Correlation Coefficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% time sensor values 70-180 mg/dl</td>
<td>0.67</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean sensor glucose value</td>
<td>-0.60</td>
<td>0.007</td>
</tr>
<tr>
<td>% time sensor ≤34 mg/dL</td>
<td>-0.049</td>
<td>0.84</td>
</tr>
<tr>
<td>% time sensor values 54-69 mg/dL</td>
<td>0.17</td>
<td>0.50</td>
</tr>
<tr>
<td>% time sensor values ≥70 mg/dL</td>
<td>-0.67</td>
<td>0.002</td>
</tr>
<tr>
<td>Standard deviation of sensor glucose values</td>
<td>-0.54</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Supported by: American Diabetes Association/Pathway to Stop Diabetes (1-15-ACE-27)
**978-P**

Meta-analysis vs. Single Trial (OpT2mise Study) Data to Assess Cost-Effectiveness of Simple CSI Devices in T2DM in the U.S.

PETER WAHLqvist, JAY L. WARNER, JOHN C. PICKUP, Cardiff, United Kingdom, Marlborough, MA, London, United Kingdom

Continuous subcutaneous insulin infusion (CSI) in T2DM improves HbA1c and reduces insulin dosage vs. multiple daily injections (MDI). However, for T2DM traditional CSI can be costly and overly sophisticated. Emerging evidence shows T2DM can be treated with limited numbers of fixed basal rates and simple bolusing (‘simple CSI’), e.g., PAQ®, a 3-day wearable device (CeDor Corporation, Marlborough, MA), as alternatives to traditional CSI. This analysis investigated cost-effectiveness in the U.S. of simple CSI vs. MDI in poorly controlled T2DM, assuming similar efficacy of traditional and simple CSI. The analysis used data from a systematic review of relationships between reduced HbA1c and increased life-expectancy and quality-adjusted life-years (DALYs). Relationships between baseline HbA1c and simple CSI vs. MDI HbA1c treatment difference based on data from either a 5-trial meta-analysis or a large single trial (OpT2mise study). Incremental cost-effectiveness ratios (ICERs) per QALY gained were below 1xGDP per capita. (2016 USD $7,467) were defined as ‘highly cost-effective’ and below 3xGDP as ‘cost-effective’. This meta-analysis shows, simple CSI devices can be cost-effective below a unit cost $18, and below $25 per patient per day using OpT2mise data. In either case, simple CSI is potentially a highly cost-effective treatment option in poorly controlled T2DM.

**Figure.**

Value of a simple CSS device by baseline HbA1c (USD per patient per day)

---

**979-P**

Dosing Time of Insulin Tregopil, a Novel Oral Insulin, in Type 2 Diabetes Mellitus Patients and Its Pharmacodynamic Effect

ANAND P. KHEDKAR, VINU JOSE, HAROLD E. LEBOWITZ, ALAN D. CHERINGTON, GILBERT ALEXANDER FLEMING, SANDEEP N. ATHALYE, ASHWINI VISHWESWARAMURTHY, Bangalore, India, Brooklyn, NY, Nashville, TN, Hapers Ferry, WV

Our aim was to evaluate pharmacodynamics (PD) of insulin tregopil (IN-105) in relation to pre-meal dosing time in type 2 diabetes mellitus (T2DM) patients in a randomized, placebo-controlled, crossover study. Fifteen patients were randomized to 5 sequences (3 patients each) and administered 4 treatments (Insulin tregopil 30 mg given 30, 20 and 10 minutes before American diabetes association (ADA) meal and placebo given 20 minutes before ADA meal) in a partial replicate crossover fashion with a washout period of 1-2 days between periods. PD sampling was done from dosing to 180 min post-meal. AU(Cmax) (glucose exposure), Cmin (minimum glucose concentration observed in the sampling period) and t1/2 (indicating time of peak PD effect) are presented in Table 1. Maximal reduction in plasma glucose (difference between baseline [meal administration] and minimum post-meal plasma glucose concentration) was 15.7 mg/dL, 9.5 mg/dL and 9.7 mg/dL for 30, 20 and 10 minutes groups, respectively. This peak PD effect was observed 16 to 37 minutes post-meal, indicating ultra-short action profile. Insulin tregopil given orally 10-20 minutes before meals has rapid onset of action. It results in effective lowering of post-meal glucose exposure with peak PD effect early in the post-meal period, hence minimizing chances of hypoglycaemia.

**Table 1. Pharmacodynamic Parameters for Plasma Insulin Tregopil.**

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Baseline-Corrected Plasma Glucose (Relative to time of Meal Administration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-180 min (mg*min/mL) &amp; SD</td>
<td>Cmin (mg/mL) &amp; SD</td>
</tr>
<tr>
<td><strong>Insulin tregopil 10 min</strong></td>
<td>217.39 (31.58)</td>
</tr>
<tr>
<td><strong>Insulin tregopil 20 min</strong></td>
<td>227.04 (67.89)</td>
</tr>
<tr>
<td><strong>Insulin tregopil 30 min</strong></td>
<td>267.67 (46.81)</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>251.96 (39.11)</td>
</tr>
</tbody>
</table>

---

**980-P**

Functionality Evaluation of Investigational Continuous Subcutaneous Insulin Infusion (CSI) Set vs. Commercially Available Sets—Assess and Surface of 3D Volume and Surface Area over Eight Days


Over 1 million people with diabetes use insulin pumps and insert a new continuous subcutaneous insulin infusion (CSI) set every 2-3 days for adequate blood glucose control. Insulin absorption from the subcutaneous tissue is slow and varies over time. This can lead to complications such as hypoglycemia and diabetic ketoacidosis. Furthermore, the repeated trauma of insertion contributes to scar tissue formation and may result in infusion site loss. The development of an extended-wear CSI infusion set that can improve the safety and efficacy of CSI therapy would be a major advantage and facilitate proper glycemic control for diabetic patients. A prototype infusion set was developed using a soft polymer material with multiple ports and tested against commercially available single-port infusion sets in an ambulatory large swine. Infusion sets were inserted into the subcutaneous tissue every other day for 8 days. A 70µL bolus of insulin and contrast agent was infused through each cannula 5 minutes prior to excision, then specimens were frozen and Micro-CT imaged. The 3D distribution and surface area of contrast agent in contact with adjacent vascular tissue were evaluated. We hypothesized that multiple-ports would increase fluid dispersion, allowing the insulin to reach more functional capillary and lymph vessels. Investigational sets had a statistically significant larger surface area (p=0.005) and volume (p=0.001) of contrast agent spread when compared with commercial sets. The design and development of a next-generation infusion set. Clinical translation of this investigational design could result in a reliable insulin delivery system that simplifies diabetes management, improves quality of life, and benefits clinical outcomes.

**Supported By:** JDRF

---

**981-P**

Insulin Pump Therapy—Patient and Provider Perceptions

MAGALY PEREZ-NIEVES, COLLEEN GAREY, LUDI FAN, ALICIA H. MCAULIFFE-FOGARTY, Indianapolis, IN, Boston, MA

This study aimed to identify the benefits and challenges of insulin pump therapy from both the patient and provider perspective. One hundred current multiple daily injection (MDI) users, including 31 former pump users, and 250 current pump users were recruited from myGlu.org, and 61 healthcare providers were recruited from T1D Exchange Clinic Network and American Association of Diabetes Educators to complete an online survey. Reports of decreased HbA1Cs (A1C) after pump initiation differed significantly between patients and providers (p = 0.001); more former users reported their AIC increased compared to current users (p = .03). Significantly more current and MDI had recent A1C < 7.0% than former users (p = 0.005).
The most common reason patients reported stopping pump therapy was an increase in blood glucose; however, providers reported that the most common reason for patients to stop pump therapy was cost. Overall 90% of current users were satisfied with their pump and providers report that 92% of their patients were satisfied with their pump; however, only 28% of former pump users reported that they were satisfied with their pump.

HCP’s perceptions of the patients’ experience with pumps differs from patients’ experience, which highlights the importance of patient-centered communication to understand an individual patient’s preferences, and challenges in managing diabetes to select an insulin treatment plan that meets both patient and HCP goals.

Conclusion: Preliminary findings suggest that learning in this technologically complex field is facilitated by social and relational practices between peers. Commercial and DIY hybrid and closed loop APSs will become increasingly common: it is therefore important to consider how people with diabetes learn to operate these systems, including the potential of peer-to-peer learning.

### 982-P

**Multiple Oral Insulin (ORMD-0801) Doses Elicit a Cumulative Effect on Glucose Control in T2DM Patients**

**ROY ELDOR, JOEL NEUDEL, KENNETH E. HOMER, MIRIAM KIDRON, Tel Aviv, Israel; Tustin, CA, Jerusalem, Israel**

Efforts to overcome the narrow therapeutic index of subcutaneously delivered insulin, have propelled the development of orally delivered alternatives. The enteric-coated ORMD-0801 oral insulin capsule has been shown to provide effective glucose control in both type 1 and type 2 diabetes patients. In this single-center, randomized, double-blind, placebo-controlled, three-way crossover study, 31 adult T2DM patients were treated with a placebo capsule during the first three days of three one-week treatment periods, followed by five days of treatment with an oral placebo (n=31) or a 460 IU insulin capsule, delivered one (qd; n=20), two (bid; n=21) or three (tid; n=20) time per day. Run-in (Days 1-3) vs. treatment (Days 4-8) period continuous glucose monitoring (CGM) data were compared, as were pre- vs. post-treatment insulin and c-peptide levels. Patients were of a mean age of 57.5±7.8, and most were male (61.3%) and Caucasian (80.6%). Mean placebo-adjusted change from baseline in 24-hour glucose (all run-in days vs. all treatment days) ranged from -7.65 mg/dL for qd to -9.91 mg/dL for tid, with a more dramatic change observed in subjects with higher glucose (>190 mg/dL; n=17) at baseline (-12.44 mg/dL (qd) and -18.43 (tid)). Pre- vs. posttreatment and placebo vs. active treatment c-peptide and insulin ratios were similar across all regimens. ORMD-0801 was well tolerated and did not elicit any serious adverse effects. The vast majority of hyperglycemic events were recorded during placebo treatment (n=27), while hypoglycemic events were evenly distributed across treatment groups (≤5/group). Thus, multiple-dose ORMD-0801 regimens safely provide for improved glucose control, which is expected to be enhanced with more extended treatment. Its impact may be of particular benefit to patients uncontrolled by current drug regimens.

### 983-P

**Learning to Close the Loop**

**HAMISH CROCKET, Hamilton, New Zealand**

The Do-It-Yourself (DIY) Artificial Pancreas System (APS) community is growing very rapidly. Initially the community was composed of members with expertise in coding and other aspects of computing. It now includes a significant proportion of members without such expertise. Building and operating a DIY APS is a complex task that, in contrast to longer established and FDA-approved therapies, is not supported by Health Care Practitioners. In the absence of professional support, how do novices learn to build and maintain a DIY APS?

Objective: To identify the key enabling and constraining factors associated with learning to build and operate a DIY APS.

Method: A Participatory Action Research approach was used. Key members of the DIY APS community were consulted in developing this study about learning in relation to DIY APS. In-depth, semi-structured interviews were conducted with 10 users of DIY APS who had built their systems in 2017. The participants in this first cohort were from multiple countries. All were adult (18+) type 1 diabetics. A thematic analysis of the interview transcripts was undertaken.

Results: Five key themes were identified. 1.) Learning was a continuation and deepening of participants’ previous peer-to-peer learning. 2.) Persistence was central to all participants’ learning. 3.) Learning was enmeshed with emotional and social support from the DIY APS community. 4.) Learning extended beyond acquiring technical skills to incorporate the collaborative, ‘pay-it-forward’ ethos of the DIY APS community.

Conclusion: Preliminary findings suggest that learning in this technologically complex field is facilitated by social and relational practices between peers. Commercial and DIY hybrid and closed loop APSs will become increasingly common: it is therefore important to consider how people with diabetes learn to operate these systems, including the potential of peer-to-peer learning.
Intradermal Administration Improves the Kinetics of Faster-Acting Fiasp® Insulin
SAHAN RANAMUKKA, IMAN MANSOOR, KIMBERLEY FENG, BORIS STOEBER, MOHAMED WHEBE, RORY ST CLAIR, CLAUDE PICHÉ, JEAN-PIERRE MOREAU, Vancouver BC, Canada; Montreal QC, Canada; Rigaud QC, Canada
Fiasp® (insulin aspart, Novo Nordisk) is a faster-acting injectable insulin formulation that is administered subcutaneously (SC) for blood glucose management. We hypothesized that intradermal (ID) administration could improve the pharmacokinetic profile of Fiasp® when compared to traditional SC injection.

Herein, we describe a simple, scalable and cost-effective hollow microneedle platform to evaluate the effects of ID administration on Fiasp® pharmacokinetics. Three groups of 8 rats received 1 IU/kg by SC injection or by ID injection using either a single or quadruple microneedle projection design. Blood was collected from 5-240 mins post-injection and assayed for insulin (ELISA, Crystal Chem) and blood glucose (hand-held glucometer) concentrations.

The results (below) show that plasma insulin levels were comparable for all groups with mean values ranging from 464 to 480 µU/mL. Yet, the peak plasma concentrations were 1.5-3-fold earlier for rats treated using the microneedle designs. This preliminary data suggests that ID injection of Fiasp® using these novel hollow microneedle designs results in faster absorption and thereby could lead to a more rapid onset of action.

Figure.

<table>
<thead>
<tr>
<th>HCL (n=11)</th>
<th>eHCL (n=11)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin Delivery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total daily insulin (units/day)</td>
<td>44 (18)</td>
<td>47 (24)</td>
</tr>
<tr>
<td>Daily basal (%)</td>
<td>55 (6)</td>
<td>55 (7)</td>
</tr>
<tr>
<td>Daily bolus (%)</td>
<td>45 (8)</td>
<td>45 (7)</td>
</tr>
<tr>
<td>Daily insulin to carbohydrate ratio</td>
<td>9.6 (3.1)</td>
<td>9.8 (3.1)</td>
</tr>
<tr>
<td>Insulin action time (hrs)</td>
<td>3.7 (0.6)</td>
<td>3.7 (0.6)</td>
</tr>
</tbody>
</table>

Glucose Metrics
| % time in 70-180mg/dL | 69 (11) | 74 (10) | 0.16 |
| Mean sensor glucose (mg/dL) | 160 (13) | 151 (11) | 0.091 |
| Time<70mg/dL (%) | 1.9 (2.4) | 1.2 (1.2) | 0.42 |
| Time<120mg/dL (%) | 0.4 (0.5) | 0.2 (0.3) | 0.21 |
| Time<180mg/dL (%) | 29 (11) | 24 (9) | 0.37 |
| Time>250mg/dL (%) | 7.3 (5.6) | 6.1 (4.7) | 0.48 |

Algorithm Related Alerts and Dropout
| Alerts (n/week) | 8.6 (5.8) | 3.9 (2.8) | 0.01 |
| CL exits (n/week) | 3.5 (3.1) | 0 (0) | 0.004 |

All results are Mean (SD); *NS= Not Significant.
Supported By: Medtronic

Optimizing Basal-Bolus Therapy in T2D—A Randomized Controlled Trial Comparing Bolus Insulin Delivery Using an Insulin Patch vs. an Insulin Pen
This multicenter RCT compared clinical, subject-reported, and safety outcomes in T2D subjects on basal insulin (A1C 7.5-11%) initiating mealtime insulin with a wearable bolus insulin delivery patch (Patch, Calibra Medical) vs. an insulin pen (Pen, NovoLog FlexPen®). The Patch was applied at least every 3 days and delivered subcutaneous bolus insulin in 2-U increments per manual click. T2D adults (N=278, age: 59.2 y, duration: 15 y), were randomized to Patch (n=139) or Pen (n=139). Baseline glargine dose was divided 1:1, basal:bolus. Using a pattern-control logbook, subjects adjusted basal and bolus insulin weekly based on fasting and pre-meal glucose targets.

Change in A1C (%) from baseline to week 24 (primary endpoint) for Patch was noninferior (p<.0001) to Pen (LS mean change of 0.0% vs. Pen, −1.60 ± 0.08) and this reduction was significant (p<.0001) in both groups. A1C improvement was maintained at 44 weeks (Figure).

There were no significant differences in adverse events, including hypoglycemia (3 severe episodes/group). In conclusion, bolus insulin delivered by Patch or Pen along with an algorithm-based weekly insulin dose titration significantly improved A1C levels in subjects with T2D, with improved patient experience and a preference for Patch.

Figure.

Supported By: Calibra Medical
Effectiveness of V-Go Wearable Insulin Delivery for Basal-Bolus Therapy—A Multicenter, Retrospective Real-World Evaluation in Type 2 Diabetes

 RIJU S. HUNDAL, STEPHAN KOWALYK, JANE CASES, AMER AL-KARADSHEH, AMANDA P. WAKIM, MELISSA DOYLE, JOHN H. SINK II, ADRIENNE SPENCE, JAMIE L. BREWER, CARLA C. NIKKEL, Newark, DE; Greensburg, PA; Marietta, OH; Houston, TX; Wheeling, WV; Erwin, NC; Macon, GA; Picayune, MS; Jackson, MS; Edmond, OK.

 With disease progression, the need to intensify therapy with insulin is often required in patients with T2D to improve glycemic control. Addressing the manner in which insulin is delivered may impact outcomes. The purpose of this study was to broadly evaluate the clinical benefits of switching from insulin delivery via insulin pen/syringe to a wearable insulin delivery device (V-Go) in patients with T2D across multidisciplinary investigators spanning 8 states. A retrospective analysis of electronic medical records evaluated change in A1C, insulin total daily dose (TDD) and weight in 283 patients. Baseline mean ± SD characteristics were A1C 9.2 ± 1.5%, BMI 34.8 kg/m² ± 6.7, weight 221 ± 45 lbs and TDD 76 ± 47 u/day (range 14 to 300) with basal-bolus (n=192, 68%), basal (n=64, 23%) and premix (n=15, 5%) regimens being predominately prescribed. Concomitant anti-hyperglycemic agents were prescribed in 77% of patients with a mean of 1.7 ± 0.8 agents/patient prescribed. Effect of V-Go was evaluated following a mean duration of 2.9 ± 1.3 and 71 ± 3.0 months of use. Significant decreases in A1C and TDD were observed at both time points. Change in weight was significant (p=0.0001) at the first time point, however, was not significant (p=0.106) by the second time point. Switching to insulin delivery with V-Go proved clinically beneficial compared to prior therapy.

Achievement of Glycemic Targets when Switching from Basal-Bolus Therapy to V-Go for Insulin Delivery in Type 2 Diabetes

 RIJU S. HUNDAL, STEPHAN KOWALYK, JANE CASES, AMER AL-KARADSHEH, AMANDA P. WAKIM, MELISSA DOYLE, JOHN H. SINK II, ADRIENNE SPENCE, JAMIE L. BREWER, CARLA C. NIKKEL, Newark, DE; Greensburg, PA; Marietta, OH; Houston, TX; Wheeling, WV; Erwin, NC; Macon, GA; Picayune, MS; Jackson, MS; Edmond, OK.

Achieving A1C targets is a fundamental component of quality measures such as HEDIS and Star ratings. A typical basal-bolus insulin regimen requires 4 insulin injections a day. Adherence decreases as the number of injections increases and non-adherence to therapy is a primary reason for failure to achieve glycemic control. Less invasive options for insulin delivery may improve patient adherence leading to positive clinical outcomes. This multi-state retrospective analysis evaluated the achievement of glycemic targets compared to prior therapy in 186 patients switched from a basal-bolus regimen to a 24-hour wearable insulin delivery device (V-Go). At baseline, mean A1C was 9.1%, weight 219 lbs and insulin total daily dose (TDD) was 84 ± 27 u/day across a mean of 4.3 injections/day. Forty-five percent of patients were poorly controlled (A1C > 9%) and less than 30% had achieved an A1C < 8% despite basal-bolus therapy. After 7 months of V-Go use, changes from baseline in A1C and TDD were significant (P<0.0001). Mean change (95% Cl) in A1C was −1.0% (−1.24, −0.78) and TDD was reduced by 32% or 25 ± 27 u/day (range 91, 137). Weight did not significantly change. Switching to V-Go, resulted in significant improvement to achievement of glycemic targets (90% increase in A1C values < 8% and 50% decrease in A1C values > 9%) compared to prior basal-bolus regimen, having positive implications on quality metrics.

Achieving A1C targets is a fundamental component of quality measures such as HEDIS and Star ratings. A typical basal-bolus insulin regimen requires 4 insulin injections a day. Adherence decreases as the number of injections increases and non-adherence to therapy is a primary reason for failure to achieve glycemic control. Less invasive options for insulin delivery may improve patient adherence leading to positive clinical outcomes. This multi-state retrospective analysis evaluated the achievement of glycemic targets compared to prior therapy in 186 patients switched from a basal-bolus regimen to a 24-hour wearable insulin delivery device (V-Go). At baseline, mean A1C was 9.1%, weight 219 lbs and insulin total daily dose (TDD) was 84 ± 27 u/day across a mean of 4.3 injections/day. Forty-five percent of patients were poorly controlled (A1C > 9%) and less than 30% had achieved an A1C < 8% despite basal-bolus therapy. After 7 months of V-Go use, changes from baseline in A1C and TDD were significant (P<0.0001). Mean change (95% Cl) in A1C was −1.0% (−1.24, −0.78) and TDD was reduced by 32% or 25 ± 27 u/day (range 91, 137). Weight did not significantly change. Switching to V-Go, resulted in significant improvement to achievement of glycemic targets (90% increase in A1C values < 8% and 50% decrease in A1C values > 9%) compared to prior basal-bolus regimen, having positive implications on quality metrics.

Clinical Outcomes with V-Go in Type 2 Diabetes Based on Duration of Diabetes

 JANE CASES, STEPHAN KOWALYK, RIJU S. HUNDAL, AMER AL-KARADSHEH, AMANDA P. WAKIM, MELISSA DOYLE, JOHN H. SINK II, ADRIENNE SPENCE, JAMIE L. BREWER, CARLA C. NIKKEL, Newark, DE; Greensburg, PA; Marietta, OH; Houston, TX; Wheeling, WV; Erwin, NC; Macon, GA; Picayune, MS; Jackson, MS; Edmond, OK.

A retrospective analysis was conducted to determine if duration of diabetes impacted clinical outcomes when switching from insulin pens/syringes to a wearable insulin delivery device (V-Go) in patients inadequately controlled. Patients (N=186) with T2D were stratified based on known duration of diabetes. A1C and insulin total daily dose (TDD) were extracted at baseline and two follow-up visits for each stratum. Paired t-tests were used to compare changes in A1C and TDD and a one-factor repeated measures ANCOVA model was performed to test for differences between groups with duration of diabetes as the factor and the corresponding baseline measure- ment as the covariate. Seventy-two percent of patients switched to V-Go had been diagnosed with diabetes for ≥ 10 years and 58% were switched to V-Go from conventional basal-bolus therapy. Clinical outcomes on V-Go were evaluated after a mean of 3 and 7 months. Regardless of duration of diabetes strata, significant reductions in A1C from baseline were observed. Further, all strata benefited from reductions in TDD with the exception of the duration stratum with the lowest baseline TDD (15 to 20 years), which maintained similar dosing on V-Go compared to baseline. By 7 months, no between group differences were observed for changes in A1C or TDD when controlling for baseline measurements. Insulin delivery with V-Go proved clinically beneficial regardless of duration of diabetes.

Achievement of Glycemic Targets when Switching from Basal-Bolus Therapy to V-Go for Insulin Delivery in Type 2 Diabetes

 RIJU S. HUNDAL, STEPHAN KOWALYK, JANE CASES, AMER AL-KARADSHEH, AMANDA P. WAKIM, MELISSA DOYLE, JOHN H. SINK II, ADRIENNE SPENCE, JAMIE L. BREWER, CARLA C. NIKKEL, Newark, DE; Greensburg, PA; Marietta, OH; Houston, TX; Wheeling, WV; Erwin, NC; Macon, GA; Picayune, MS; Jackson, MS; Edmond, OK.

Achieving A1C targets is a fundamental component of quality measures such as HEDIS and Star ratings. A typical basal-bolus insulin regimen requires 4 insulin injections a day. Adherence decreases as the number of injections increases and non-adherence to therapy is a primary reason for failure to achieve glycemic control. Less invasive options for insulin delivery may improve patient adherence leading to positive clinical outcomes. This multi-state retrospective analysis evaluated the achievement of glycemic targets compared to prior therapy in 186 patients switched from a basal-bolus regimen to a 24-hour wearable insulin delivery device (V-Go). At baseline, mean A1C was 9.1%, weight 219 lbs and insulin total daily dose (TDD) was 84 ± 27 u/day across a mean of 4.3 injections/day. Forty-five percent of patients were poorly controlled (A1C > 9%) and less than 30% had achieved an A1C < 8% despite basal-bolus therapy. After 7 months of V-Go use, changes from baseline in A1C and TDD were significant (P<0.0001). Mean change (95% Cl) in A1C was −1.0% (−1.24, −0.78) and TDD was reduced by 32% or 25 ± 27 u/day (range 91, 137). Weight did not significantly change. Switching to V-Go, resulted in significant improvement to achievement of glycemic targets (90% increase in A1C values < 8% and 50% decrease in A1C values > 9%) compared to prior basal-bolus regimen, having positive implications on quality metrics.

We retrospectively evaluated the clinical outcomes on V-Go after a mean duration of 2.9 ± 1.3 and 71 ± 3.0 months of use. Regardless of duration of diabetes strata, significant reductions in A1C from baseline were observed. Further, all strata benefited from reductions in TDD with the exception of the duration stratum with the lowest baseline TDD (15 to 20 years), which maintained similar dosing on V-Go compared to baseline. By 7 months, no between group differences were observed for changes in A1C or TDD when controlling for baseline measurements. Insulin delivery with V-Go proved clinically beneficial regardless of duration of diabetes.
Late and Missed Meal Boluses with Multiple Daily Insulin Injections
LISA M. NORGANDER, STACEY ANDERSON, CAROL J. LEVY, LAYA EKHLASPOUR, DAVID W. LAM, LIANA HSU, SARAH E. LOEBNER, SELASIE J. OGYAADU, GREGOIRE D. MALLETTE, CAMILLA M. LEVISTER, MARC D. BRETON, BRUCE BUCKINGHAM, Palo Alto, CA; Charlottesville, VA, New York, NY, Stanford, CA

Background: Using sensor augmented pump data, late or missed meal boluses have shown a strong correlation with higher A1c levels, particularly in adolescents. With the Type Zero InControl Phone connected to a Dexcom G5 sensor and Novo insulin pens with memory and connectivity it is now possible to evaluate for late and missed meal boluses in MDI users.

Methods: For this study 326 days of CGM data were evaluated from 24 subjects (mean age 32, range 15-59 years). Seven days of data were analyzed on starting the system and 7 days 1 month later. Overall 1,173 meals were evaluated. Meals were determined by either the subject manually recording the meal, or if the CGM was >70 mg/dl and there was a >70 mg/dl rise within 2 hours. A late meal bolus was defined when the CGM increased >50 mg/dl from baseline prior to an insulin dose. A missed meal bolus was defined by no insulin dose within 2 hours from the start of the CGM rise.

Results: 27% (range 8 to 55%) of meals had either a late or missed meal boluses: 13% (range 2-30%) were late and 14% (range 2 to 38%) were missed. There was no correlation with age or gender. There was a positive correlation with the percentage of missed meal boluses and A1c levels (p<0.01), but no correlation with the percentage of late meal boluses and A1c levels. There were no significant differences in missed or late meal boluses when comparing the first week of use to using the system one month later.

Conclusion: The rate of late or missed meal boluses is high for both adults and adolescents using MDI therapy, and missed meal boluses correlated with higher A1c levels. Having this information may provide significant insight to patients and help clinicians provide advice to MDI patients.

Supported By: The Leona M. and Harry B. Helmsley Charitable Trust

Real-World Data from the MiniMed™ 670G System Commercial Launch—The First 1,052 Patients Using the System for Three Months

PRATIK AGRAWAL, MICHAEL STONE, SHWETA GOPALAKRISHNAN, CATHERINE FOGEL, SCOTT W. LEE, FRANCINE R. KAUFMAN, Northridge, CA

The Medtronic MiniMed™ 670G hybrid closed-loop system with SmartGuard™ technology was released for commercial use in the U.S. in March 2017. Sensor glucose (SG) and device utilization data from the initial open-loop Manual Mode and closed-loop Auto Mode periods were analyzed for the first 1052 patients and compared to those from the MiniMed™ 670G system pivotal trial.

De-identified data voluntarily uploaded to CareLink™ Personal software, from 3/17/17 to 11/11/17, were evaluated monthly, for 3 months. Data for 12,758 patient-days in Manual Mode and 142,065 patient-days after Auto Mode start were compared to results of the MiniMed™ 670G pivotal trial (124 patients aged 14-75 years) conducted from 6/2/15 to 3/7/16.

The percentage of time in Auto Mode, after initiation, was >85% over the 3 months for the entire commercial cohort. The SG values across glucose ranges were comparable to pivotal trial data (Table). These findings indicate that outcomes data for the first 1052 patients using the commercial MiniMed™ 670G system mirrored the pivotal trial outcomes. Further, the increased time in target range and decreased hypoglycemia and hyperglycemia were sustained over 3 months.
Clinical Diabetes/Therapeutics

POSTERS

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—INSULINS

Table.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 1</td>
<td>124</td>
<td>124</td>
<td>1052</td>
<td>1052</td>
<td>1052</td>
<td>1052</td>
<td>1052</td>
<td>1052</td>
<td>1052</td>
</tr>
<tr>
<td>Month 2</td>
<td>150.2</td>
<td>150.7</td>
<td>157.0</td>
<td>149.8</td>
<td>150.3</td>
<td>150.75</td>
<td>150.2</td>
<td>150.75</td>
<td>150.75</td>
</tr>
<tr>
<td>Percentage of time in SG range, mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>0.85</td>
<td>0.52</td>
<td>0.38</td>
<td>0.30</td>
<td>0.32</td>
<td>0.33</td>
<td>0.85</td>
<td>0.52</td>
<td>0.38</td>
</tr>
<tr>
<td>&gt;50</td>
<td>1.33</td>
<td>0.78</td>
<td>0.60</td>
<td>0.46</td>
<td>0.50</td>
<td>0.52</td>
<td>1.33</td>
<td>0.78</td>
<td>0.60</td>
</tr>
<tr>
<td>&gt;70</td>
<td>2.47</td>
<td>2.96</td>
<td>2.65</td>
<td>2.07</td>
<td>2.21</td>
<td>2.23</td>
<td>2.47</td>
<td>2.96</td>
<td>2.65</td>
</tr>
<tr>
<td>&gt;180</td>
<td>67.13</td>
<td>72.61</td>
<td>67.39</td>
<td>75.00</td>
<td>74.36</td>
<td>74.07</td>
<td>67.13</td>
<td>72.61</td>
<td>67.39</td>
</tr>
<tr>
<td>&gt;250</td>
<td>6.94</td>
<td>5.59</td>
<td>7.48</td>
<td>4.90</td>
<td>4.88</td>
<td>5.14</td>
<td>6.94</td>
<td>5.59</td>
<td>7.48</td>
</tr>
</tbody>
</table>


995-P

User- and Health Care Provider-Reported Outcomes for a Wearable Bolus Insulin Delivery Patch


This multicenter RCT compared efficacy, safety, and User-/HCR-reported outcomes for adults with T2D (Users, A1c: 7.5-11%) on basal insulin initiating mealtime insulin with a wearable bolus insulin delivery patch (Patch, Calibra Medical, n=139) vs. an insulin pen (Pen, NovoLog FlexPen®, n=139). The Patch was applied at least every 3 days and delivered subcutaneous bolus insulin in 2-U increments per manual click.

Study duration was 48 weeks with cross-over at week 44; 88% (Patch) and 86% (Pen) of Users completed week 24 assessments; 77% and 76% completed week 48 assessments. Treating HCPs (N=99) rated their experience with Patch at week 24.

Change in A1C (%) from baseline to week 24 (primary endpoint) showed noninferiority of Patch vs. Pen (p<0.001). Change in User satisfaction (measured by the Insulin Delivery System Rating Questionnaire) at week 24 favored Patch over Pen for all measures; comparisons for convenience and overall satisfaction were significant (p<0.01). Change in User quality of life (measured by the Diabetes-Specific Quality of Life Questionnaire) at week 24 favored Patch over Pen for 6/7 measures; comparisons for daily functions and diet restrictions were significant (p<.05). Comparisons of User experience ratings at week 24 favored Patch over Pen for all 11 items; of those showed a significant difference (p<0.01). At week 48, User preferences for Patch over Pen among those who had used Patch for 44 weeks ranged from 72% to 82%, 69% wanted to change from Pen to Patch. Results were similar but less pronounced for those who had used Patch for 4 weeks.

HCP questionnaire ratings for clinical appropriateness of Patch at week 24 ranged from 67% to 85% in favor. Additionally, 74% rated training for Patch use as “easy” and 89% reported that it took ≤30 minutes; 91% of HCPs preferred Patch over Pen for initiating mealtime insulin.

These results suggest that Patch is a viable alternative to Pen for meal-time insulin; both Users and HCPs preferred Patch to Pen.

996-P

Beta-Cell Function Improved in Insulin Deficient Type 2 Diabetics and Insulin Sensitivity Improved in Insulin-Resistant Type 2 Diabetics during Long-Term Insulin Pump Therapy

SOO BONG CHOI, EUN SHIL HUNG, YUN HEE NOH, Seoul, Republic of Korea.

We wanted to investigate the changes in beta cell function and insulin sensitivity during long-term CSII therapy in patients with type 2 diabetes (T2D) up to for 3 years. We discontinued oral antidiabetic drugs and applied CSII therapy to T2D patients (number, 110 with 64% of male; age, 59.9 ± 9.1 years; duration, 12.0 ± 9.2 years; HbA1c 8.9 ± 2.0%; BMI 23.5 ± 2.5 kg/m²). Blood samplings were performed yearly for 3 years at overnight fasting and 120 minutes after ingestion of a standard mixed meal (500 kcal). Serum C-peptide, glucose, and HbA1c were measured, and Matsuda Index (MI) were calculated. The patients were grouped into high MI (insulin sensitive group) and low MI (insulin resistant group) by the mean value of baseline MI. Mean HbA1c decreased significantly from 8.9% to 6.5% and there was no difference in glycemic control between the two groups.

In insulin sensitive group, mean serum C-peptide increased significantly during CSII therapy. In contrast, mean serum C-peptide did not change but mean MI increased significantly in insulin resistant group (Fig. 1).

In conclusion, by the physiological delivery of insulin using insulin pumps, the two main pathophysiology of T2D, either insulin deficiency or insulin resistance, seemed to be corrected, respectively.

Fig.1. The serum C-peptide and Matsuda Index changes in insulin sensitive and insulin resistant type 2 diabetics by insulin pump therapy for 3 years.

Moderated Poster Discussion: Insulin Marches On (Posters: 997-P to 1002-P). see page 22.

997-P

Efficacy of IDeGliira vs. Basal-Bolus Therapy in Subjects with Type 2 Diabetes in DUAL VII by Baseline Characteristics

LIANA K. BILLINGS, DAVID C. KLOFFON, NIKOLAOS TENTOLOURIS, RANDI GRØN, NATALIE HALLADIN, ESTEBAN JODAR, Evanston, IL, San Mateo, CA, Athens, Greece, Seborg, Denmark, Madrid, Spain.

In SOB subjects with type 2 diabetes uncontrolled on metformin and basal insulin, the DUAL VII trial (NCT02420262) demonstrated that a once-daily injection of insulin degludec/liraglutide (IDeGliira) was non-inferior to multiple injections of basal-bolus therapy (insulin glargine 100 units/mL + insulin aspart before each main meal) for A1C reduction, and was associated with a significantly lower risk of hypoglycemia. This non-prespecified post-hoc analysis examined whether the efficacy results persisted across sub-groups for six different variables and evaluated whether benefits seen in the trial were applicable across a broad patient population. After 26 weeks of treatment, there was no significant difference in A1C reduction between IDeGliira compared with basal-bolus in any baseline characteristic group (A1C, BMI, age, diabetes duration, total daily insulin dose and fasting plasma glucose (Table)). Additionally, there was no significant interaction between treatment and baseline sub-group for any of the baseline characteristics (Table).

In conclusion, the A1C lowering was comparable between once-daily IDeGliira vs. basal-bolus therapy after 26 weeks of treatment, irrespective of baseline characteristics, which underscores the general application of these findings to a broad patient population.
**Fasting Plasma Glucose Indicates Reversibility of Acute Insulin Response after Short-Term Intensive Insulin Therapy in Patients with Type 2 Diabetes of Various Duration**

**LIEHUA LIU, STYUE YANG, JIAJIN LIU, LI HAI, JUAN LIU, YANDING LI, GUANG-ZHOU, CHINA; HONG KONG, CHINA; MUNICH, GERMANY; ZHU JIAN, CHINA; KONISHI YASUSHI, JAPAN; HONG KONG, CHINA; LUND, SWEDEN; MINNEAPOLIS, MN, USA; HONG KONG, CHINA; JERUSALEM, ISRAEL; SÜRBORGH, DENMARK; CHAPEL HILL, NC, USA; JERUSALEM, ISRAEL; MÜNSTER, GERMANY; TÓKYO, JAPAN; MINNEAPOLIS, MN, USA; AUCKLAND, NEW ZEALAND; MÉLYNI, HUNGARY; ZHOU ZHOU, CHINA; ZHANG QIN, CHINA; HONG KONG, CHINA; MELBOURNE, AUSTRALIA; Helsingborg, Sweden; Søborg, Denmark; Tokyo, Japan.**

**Objective:** In patients with early type 2 diabetes, short-term intensive insulin therapy (SIIT) reverses β cell dysfunction measured by acute insulin response (AIR). However, the complicated procedures limit large-scale use of AIR. Also unclear is whether SIIT is effective in patients with longer duration. This study is performed to assess fasting indicators estimating recovery of AIR after SIIT for type 2 diabetes of various duration.

**Research Design and Methods:** Patients with type 2 diabetes (n=62) who had poor glycemic control were enrolled. Near-normoglycemia was achieved and maintained for 7 days with insulin pump. AIR was measured by intravenous tolerance tests before and after SIIT.

**Results:** Both fasting plasma glucose (FG, 12.0 ± 3.0 vs. 7.71 ± 1.6 mmol/L, P<0.001) and 2h-postprandial glucose (17.3 ± 5.2 vs. 11.5 ± 3.7 mmol/L, P<0.001) decreased significantly after SIIT. AIR was improved from -16.7 (-117.4, 52.4) pmol/L·min to 178.7 (31.8, 390.7) pmol/L·min (P<0.001). Increase of AIR (ΔAIR) was observed in all disease duration categories (329.2 ± 380.0, 312.8 ± 347.8, and 123.8 ± 186.3 pmol/L·min for patients with disease duration of <2 years, 2-6 years, and >6 years respectively, P=0.10). AIR was almost absent when FPG was over 10 mmol/L. However, when FPG was 6-9 mmol/L, AIR was almost normal. AIR could not be estimated when FPG was over 9 mmol/L.

**Conclusions:** Recovery of AIR could be obtained in patients with various duration of type 2 diabetes, and it could be estimated conveniently by FPG and other fasting indicators.
A1C, was confirmed for mealtime and post-meal FA vs. IAasp (Figure). Meal-
time FA was superior to IAasp for 1-h PPG increment using a standard meal
test (ETD: -0.90 [-1.38; -0.45] mmol/L; -16.24 [-24.42; -8.05] mg/dL). Self-mea-
 sured 1 hour PPG increment favored FA at breakfast (ETD: -0.58 [-0.99; -0.17]
mmol/L; -10.43 [-17.85; -3.02] mg/dL) and across all meals (ETD: -0.49 [-0.74;
-0.21] mmol/L; -8.58 [-13.35; -3.81] mg/dL). No significant differences were
observed in treatment-emergent adverse events or overall rate of severe or
confirmed hypoglycemic episodes (PG <3.1 mmol/L [56 mg/dL]), but signifi-
cantly less hypoglycemia was seen 3 to 4 h after meals with mealtime FA.
In summary, mealtime FA provided superior PPG control to IAasp with a
similar overall improvement in A1C and no increased safety risk. These find-
ings were consistent with those previously reported in subjects with T1D.

In conclusion, BC Combo demonstrated superior PPG control in T2DM sub-
jects with numerically fewer subjects experiencing symptomatic hypoglyce-
mic late prandial phase (2-6 h) than LMx and G+L. The total insulin PK profile
of BC Combo was numerically better than LMx (32.4%) vs. LMx (32.4%) and G+L (21.6%). The proportion of subjects experiencing documented symptomatic hypoglycemic events (plasma glucose <70 mg/dL) over 24h was numerically lower with BC Combo (15.8%) vs. LMx (32.4%) and G+L (21.6%). The total insulin PK profile
of BC Combo showed a faster time to insulin peak and a lower exposure in the
late prandial phase (2-6 h) than LMx and G+L.

In conclusion, BC Combo demonstrated superior PPG control in T2DM sub-
jects with numerically fewer subjects experiencing symptomatic hypoglycemia
compared to both LMx and separate G+L.

**Figure. Mean A1C over time**

![Error bars: ± standard error (mean). Changes from baseline in A1C were analyzed using a multiple imputation model.](image1)

**Supported By:** Novo Nordisk

---

**1002-P**

**Effect of the Combination Therapy of Liraglutide, a GLP-1 Receptor Analog, and IDegAsp in Patients with Type 2 Diabetes**

**MARINA HARADA, MINORI SHINDA, RIKI SAKAMOTO, JUN SUZUKI, KENICHI 
TAKAHASHI, TADASHI YAMAKAWA, Yokohama, Japan**

**Background:** Diabetes care management aims to not only achieve good
glycemic control but also maintain the quality of life (QoL). Basal insulin-
treated patients frequently receive bolus insulin as a strengthening therapy; 
however, concerns exist about QoL due to the increasing number of injec-
tions. We examined the glycemic effect and QoL in patients treated with 
liraglutide (Lira) and insulin degludec/insulin aspart (IDegAsp).

**Methods:** Patients with type 2 diabetes treated with basal-supported oral 
therapy (BOT) and DPP-4 inhibitor were enrolled in this observational study. 
Basal insulin was switched to IDegAsp at the same dose and DPP-4 inhibitor 
to Lira simultaneously; no titration protocol was used. We estimated the
clinical and laboratory parameters and assessed the change in QoL within
12 weeks using the diabetes therapy-related QoL (DTR-QoL) questionnaire.
The timing of dose up in regard to IDegAsp and Lira was also determined.

**Results:** Fourteen patients were enrolled (male/female: 9/5, age (years): 
63.6). The IDegAsp dose ranged from 0.1 to 13.7 U, all patients received 0.9 mg/day of Lira. The combination therapy significantly decreased HbA1c
levels (8.7% vs. 7.1%, P=0.02), pre-breakfast glucose level (138.2 mg/dL vs. 
108.9 mg/dL, P=0.044), bodyweight (62.9 kg vs. 60.3 kg, P=0.003), and BMI (24.6 vs. 23.5, P=0.004). The total DTR-QoL score at baseline was 61.6 and
significantly improved to 75.2 (P=0.004). Significant improvement was also 
seen in D3 score (hypoglycemia: 63.6 vs. 81.4, P=0.038). D4 score (satisfac-
tion with treatment) showed an increasing trend (59.0 vs. 78.2) and was
negatively correlated with HbA1c levels (P=0.049). The combination is called 
BOTH or DPP-4 inhibitor were enrolled in this observational study. 
Lira and IDegAsp significantly improved glycemic control and reduced the body-
weight without deteriorating QoL in type 2 diabetes, although the treatment 
modality changed from one-injection to two-injection therapy.

**1003-P**

**Comparison of Ultra-Rapid-Acting Insulin's Effect—Randomised, 
Triple Crossover Study**

**SODIHI TAKEISHI, HIROKI TSUBOI, SHIDOO TAKEKOSHI, 
Inawama, Japan**

We investigated which ultra-rapid acting insulin (URI) is the most effec-
tive in improving glycemic variability (GV)- insulin glulisine (IG), insulin lispro 
(L) or insulin aspart (A). We calculated a required sample size of 12. Thirty 
type 2 diabetic patients were randomly allocated to 3 groups. On admission, 
prebreakfast and bedtime glucose levels (PBGL) were stabilised at 80 mg/dL 
level with URI (before wearing continuous glucose monitoring (FreeStyle 
Libre Pro) device (FLP); G) and insulin glargin 300 U/mL (IDegAsp) during 
the study period. Group 1: PBGL were maintained at 80 mg/dL level with 
URI; group 2: PBGL were maintained at 80 mg/dL level with IDegAsp; group 3: 
PBGL were maintained at 80 mg/dL level with Lira. The combination therapy 
significantly decreased HbA1c levels (8.7% vs. 7.1%, P=0.02), pre-breakfast glucose level (138.2 mg/dL vs. 108.9 mg/dL, P=0.044), bodyweight (62.9 kg vs. 60.3 kg, P=0.003), and BMI (24.6 vs. 23.5, P=0.004). The total DTR-QoL score at baseline was 61.6 and
significantly improved to 75.2 (P=0.004). Significant improvement was also 
seen in D3 score (hypoglycemia: 63.6 vs. 81.4, P=0.038). D4 score (satisfac-
tion with treatment) showed an increasing trend (59.0 vs. 78.2) and was
negatively correlated with HbA1c levels (P=0.049). The conclusion is that: BOTT or DPP-4 inhibitor were enrolled in this observational study. 
Lira and IDegAsp significantly improved glycemic control and reduced the body-
weight without deteriorating QoL in type 2 diabetes, although the treatment 
modality changed from one-injection to two-injection therapy.
administered at 08:00. Data collected on the second evaluation day were analysed. Test meals were given. Increased postprandial (Po) Gl, Po glucose gradients, area over the glucose curve (c70 mg/dL) were significantly lower in patients on G, L, A, in that order. Start time of hypoglycemia occurrences (Ho) was significantly earlier and finish time of Ho was significantly later in patients on A than L. G is the best URI to improve GV.

Table.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>n</th>
<th>mean ± SD (range)</th>
<th>median</th>
<th>min/max</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gl</td>
<td>284</td>
<td>106.8 ± 38.9 (3.0-269.0)</td>
<td>102.0</td>
<td>1.0/276.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Po glucose gradient</td>
<td>284</td>
<td>5.8 ± 2.5 (0.25-7.5)</td>
<td>5.4</td>
<td>0.5/7.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Area over glucose curve</td>
<td>284</td>
<td>209.9 ± 38.9 (0.2-699.0)</td>
<td>205.0</td>
<td>1.0/699.0</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Overall improvements were seen for PCPs (n = 284) and endos (n = 57) compared to D/Es (n = 57; medium effect of V= 0.217). Relative percent changes from pre- to post-assessment of V were between 15% and 126% for PCPs and -4% to 40% for endos. While only 7% of PCPs and 19% of endos answered all 4 questions correctly on the pre-assessment, 28% of PCPs and 41% of endos answered all correctly on the post-assessment. The greatest improvements were seen in dosing strategies for preventing hypoglycemia (44% improvement in PCP, P <.001, and 18% in endos, P = 0.025), individualizing therapy in a patient with high glucose variation (23% improvement in PCP, P <.001, and 7% in endos, P = 0.4), and insulin initiation (8% improvement in PCP, P = 0.039, and 22% in endos, P = 0.058). PCPs reported a confidence level of 2.86 on the pre-assessment, 2.50 on the post-assessment for a total confidence shift of 20.6%. Endos reported a confidence level of 4.04 on the pre-assessment and 3.45 on the post-assessment, for a total confidence shift of 5.59. Endos had a higher baseline knowledge level compared to D/Es, and may need more foundational education related to follow-on basal insulin. As expected, PCPs had lower baseline knowledge compared to D/Es, and may need more foundational education related to newer therapeutic options for T2D.

Supported By: Boehringer Ingelheim; Eli Lilly and Company

---

1004-P

**Improving Appropriate Basal Insulin Use in Clinical Practice—Impact of Physician Education on T2D Clinical Management**

**AMY LARKIN, MICHAEL LACOUTURE, ANNE LE, New York, NY**

Although insulin is among the most effective antihyperglycemic agents, initiation is often delayed. We studied whether online continuing medical education (CME) could improve the clinical performance and confidence of primary care physicians (PCPs) and endocrinologists (endos) regarding use of basal insulin. The CME activity consisted of an online, 30-minute, video-based roundtable panel discussion. Educational effects were assessed using 3 case-based and 1 self-efficacy repeated pair pre-/post-assessment questions and McNemar’s chi-squared test. The activity launched online August 16, 2016, and data were collected through December 20, 2016. Overall improvements were seen for PCPs (n = 197; P <.001) and endos (n = 28, P <.001). Relative percent changes from pre- to post-assessment were between 15% and 126% for PCPs and -4% to 40% for endos. While only 7% of PCPs and 19% of endos answered all 4 questions correctly on the pre-assessment, 28% of PCPs and 41% of endos answered all correctly on the post-assessment. The greatest improvements were seen in dosing strategies for preventing hypoglycemia (44% improvement in PCP, P <.001, and 18% in endos, P = 0.025), individualizing therapy in a patient with high glucose variation (23% improvement in PCP, P <.001, and 7% in endos, P = 0.4), and insulin initiation (8% improvement in PCP, P = 0.039, and 22% in endos, P = 0.058). PCPs reported a confidence level of 2.86 on the pre-assessment, 2.50 on the post-assessment for a total confidence shift of 20.6%. Endos reported a confidence level of 4.04 on the pre-assessment and 3.45 on the post-assessment, for a total confidence shift of 5.59. Endos had a higher baseline knowledge level compared to D/Es, and may need more foundational education related to follow-on basal insulin. As expected, PCPs had lower baseline knowledge compared to D/Es, and may need more foundational education related to newer therapeutic options for T2D.

Supported By: Sanofi

---

1006-P

**Ultra-rapid Lispro (URLi) Shows Faster Absorption of Insulin Lispro vs. Humalog® during Insulin Pump (CSII) Use in Patients with T1D**

**CHRISTOF M. KAZDA, JENNIFER LEUHR, RONG LIU, THOMAS HARDY, SHOBHA REDDY, SHANE P.C. CHUA, XIAONIAN GOU, ULRIKE HSVELMANN, CHRISTOPH KAPITZA, Vagnas France, Indianapolis, IN Singapore, Singapore, Neuss, Germany**

URLi (LY900014), a novel ultra-rapid mealtime insulin in Phase 3 development, is shown to reduce postprandial glucose after subcutaneous injection. This study evaluated the pharmacokinetics and pharmacodynamics (PD) of URLi via CSII. In a double-blind, randomized cross-over study, 24 adult patients with T1D received URLi or insulin lispro (Humalog®; HL) for 3 days. Mixed meal tolerance tests (MMTT) were conducted on Days 1 and 3 after catheter insertion using a standard (1.5 U/min) single-wave bolus. URLi showed faster insulin lispro absorption on both days compared to HL. URLi reduced time to early half-maximal drug concentration by 37% ( -8.5 min) and 32% (-5.3 min) compared to HL on Days 1 and 3 (both p <0.0001). Area under the insulin lispro concentration time curve (AUC) for the first 15 min was >50% higher than HL after dosing with URLi on Days 1 and 3 (p=0.005). URLi reduced 1-hour postprandial glucose excursion of the MMTT by 45% on Day 1 (p=NS) and 47% on Day 3 (p=0.009) compared with HL (Figure). Accelerated URLi absorption was associated with trends toward lower postprandial glucose excursion for the entire MMTT (57% and 20% reductions in ΔAUC[0-9h] on Days 1 and 3, both NS). The study was not powered for PD assessment which may contribute to the lack of statistical significance. No differences were seen in the number or severity of hypoglycemic events or local tolerability between URLi and HL.

**Figure.** Mean plasma glucose concentration over time for URLi and Humalog® (a trademark of Eli Lilly and Company) on Day 1 (left) vs. Day 3 (right).
**Clinical Diabetes/Posters**

**Analysis of the AWARD-2 Clinical Trial in Patients with Different Baseline Glycemic Patterns (Based on ability of temperature range from 4 °C to room temperature had no effect on the stability of in use insulin pen. We observed the trend toward different in stability between clear insulin analog and turbid NPH insulin.**

**Supported By:** Mahidol University (R016020209)

---

**Clinical Therapeutics/New Technology—Insulins**

### 1007-P

**Treatment Effects of Once-Weekly Dulaglutide vs. Insulin Glargine in Patients with Different Baseline Glycemic Patterns (Based on High/Low Fasting or High/Low Postprandial Glucose)—A Post-Hoc Analysis of the AWARD-2 Clinical Trial**

**FRANCESCO GIORGINO, MARIA YU, AXEL HAUPF, ZVONKO MILICEVIC, LUIS-EMILIO GARCIA-PEREZ, Sari, Italy; Toronto, ON, Canada; Indianapolis, IN, Vienna, Austria**

Insulin glargine (Glar) exerts its action primarily through a decrease in fasting plasma glucose (FFP), whereas dulaglutide (DU), a once-weekly GLP-1RA, targets both fasting and postprandial glucose (PPG). This post-hoc analysis of the AWARD-2 study assessed the efficacy of DU vs. Glar in patients with type 2 diabetes with different glycemic patterns at baseline determined by self-monitoring of blood glucose (fasting glucose [FG] vs. PPG). Patients were categorized into 4 groups based on combinations of low and high FG and PPG, with median baseline values of FG (151 mg/dL) and PPG (182 mg/dL) being used as threshold for low and high, respectively. Analyses were conducted using analysis of covariance. DU showed a statistically significantly greater reduction in A1c compared with Glar for all of the subgroups, except for low FG/high PPG, where the numerical difference was in favor of DU but did not reach statistical significance (Table). Total hypoglycemia was numerically lower for DU vs. Glar in all subgroups. DU showed efficacy on A1c reductions across different baseline glycemic patterns vs. Glar (with the exception of low FG/high PPG), indicating a clinical benefit of targeting both FG and PPG, irrespective of the baseline glycemic phenotype.

**Table.**

<table>
<thead>
<tr>
<th>Group</th>
<th>FG (mg/dL)</th>
<th>PPG (mg/dL)</th>
<th>A1c (%)</th>
<th>DU vs. Glar (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low FG/low PPG</td>
<td>100 ± 15</td>
<td>100 ± 15</td>
<td>7.6 ± 1</td>
<td>0.001</td>
</tr>
<tr>
<td>Low FG/high PPG</td>
<td>100 ± 15</td>
<td>100 ± 15</td>
<td>8.0 ± 1</td>
<td>0.012</td>
</tr>
<tr>
<td>High FG/low PPG</td>
<td>150 ± 20</td>
<td>150 ± 20</td>
<td>7.5 ± 1</td>
<td>0.004</td>
</tr>
<tr>
<td>High FG/high PPG</td>
<td>150 ± 20</td>
<td>150 ± 20</td>
<td>7.8 ± 1</td>
<td>0.007</td>
</tr>
</tbody>
</table>

---

### 1008-P

**The Effect of Temperature on the Stability of In-Use Insulin Pens**

**TANAWAN KONGMALAI, LUKANA PREECHASUK, SARAWUT JUNNU, SIRIPONG TANAWAN, BANGKOK, Thailand**

Background: Improper storage of in use insulin could decrease its potency. Temperature has been shown to have an effect on the stability of insulin. Therefore, the manufacturers recommend to keep an in use insulin at the room temperature (RT), not exceeding 25-30 °C. However, The RT in tropical countries is higher than that. Thus far, there are few studies evaluate the effect of temperature on insulin stability, especially insulin pens which are widely used nowadays.

**Aim:** To investigate the effect of temperature on the stability of basal insulin after opening for 28 days.

**Methods:** There are four different commercial basal insulin pens, including long and intermediate acting insulin were evaluated (N=5 each). They were opened and stored at 3 different conditions, including: refrigerated (2-8 °C), RT and incubator (37 °C) for 28 days. An unopened insulin pens from the same batches were stored under standard condition as control (CON). During the study period, the insulin pens were well-mixed and discarded 2 units every day to mimic the daily usage of diabetes patient. The temperature logger was used to record the hourly temperature in RT. After 28 days, the amount of insulin was evaluated using the Ultra-high performance liquid chromatography assay.

**Results:** Average RT throughout the study period was 29.7 ± 2.8 °C. The percentage amount of insulin (mean ± SD) stored at 4°C, RT or 37°C, compared with CON was as follows: 99.0 ± 0.8%, 98.7 ± 2.5%, 101.1 ± 2.2% for long-acting insulin; 97.4 ± 0.7%, 97.2 ± 1.6%, 99.0 ± 2.0% for NPH-1; 101.4 ± 1.1%, 101.5 ± 2.2%, 100.7 ± 2.3% for NPH-2; and 98.7 ± 1.5%, 97.8 ± 1.1%, 98.5 ± 1.7% for NPH-3. There was no statistically significant in the difference. However, there was a trend toward different in AUC2 between long acting and NPH insulin.

**Conclusion:** Temperature, as high as 37°C, cyclic temperature and the variability of temperature range from 4 °C to room temperature had no effect on the stability of insulin pens. This study is important to promote the proper storage and handling of in use insulin pens, especially in tropical countries.

---

### 1009-P

**Ultra-rapid Lispro (URLi) Reduces Postprandial Glucose Excursions vs. Humalog® in Patients with T2D at Multiple Meal-to-Dose Timing Intervals**

**CHRISTOPH KAPITZA, JENNIFER LEHOR, RONG LIU, SHOBHA REDDY, MARY A. DELLVA, MARK MATZPOULIDIS, MARY P. KNADLER, MEI TENG LOH, THOMAS HARDY, CHRISTOF M. KAUDA, Neuss, Germany; Indianapolis, IN, London, United Kingdom, Singapore, Vagnas, France**

URLI (LY900014), a novel ultra-rapid mealtime insulin in Phase 3 development, is shown to reduce postprandial glucose after subcutaneous injection. This 2-part, randomized, double-blind, Phase 1b study evaluated differences in PK and PD between URLI and insulin lispro (Humalog®; HL) in 30 patients with T2D. Part A used a 6-period crossover design to assess safety and comparison of PK and postprandial glucose response to solid mixed meal tolerance tests (MMTT) with URLI or HL at different injection to mealtime intervals (-15, 0 and +15 min). Part B evaluated safety, PK and PD during 2 weeks of daily dosing (immediately before a meal) in a parallel design. In Part A, URLI reduced glucose excursions (assessed as change in area under the concentration curve vs. time [AUC]) during the first 2 hours (AUC0-2h) and entire 5 hours (AUC0-5h) of the MMTT regardless of dose timing (Fig). URLI reduced AUC0-2h by 31% (p=0.014), 47% (p=0.001), and 4% (p=NS) and AUC0-5h by 49% (p=0.049), 105% (p=0.001), and 28% (p=0.076) vs. HL at -15, 0 and +15 min (significance level =0.1). The PK and PD profiles for URLI and HL were sustained after 2 weeks of outpatient dosing (Part B). More hypoglycemic events occurred with URLI during MMTTs but these were mild and mostly asymptomatic. Only a few events occurred in either group during 2 weeks of outpatient dosing. Local tolerability was similar between treatments.

**Figure:** Mean glucose concentration after dosing 5 min before (left), immediately prior (middle), and 15 minutes post last meal (right) by treatment following a single dose (Part A). Humalog® is a trademark of Eli Lilly and Company.

**Table.**

<table>
<thead>
<tr>
<th>Condition</th>
<th>AUC0-2h (%)</th>
<th>AUC0-5h (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>URLI</td>
<td>47% (p=0.001)</td>
<td>105% (p=0.001)</td>
</tr>
<tr>
<td>HL</td>
<td>31% (p=0.014)</td>
<td>4% (p=NS)</td>
</tr>
</tbody>
</table>

---

### 1010-P

**Ultra-rapid Lispro (URLi) Reduces Postprandial Glucose Excursions vs. Humalog® in Patients with T1D at Multiple Meal-to-Dose Timing Intervals**

**LEONA PLUM-MOERSCHEL, JENNIFER LEHOR, RONG LIU, SHOBHA REDDY, MARY A. DELLVA, SHUFEN LIM, MEI TENG LOH, MARY P. KNADLER, THOMAS HARDY, CHRISTOF M. KAUDA, Mainz, Germany; Indianapolis, IN, Singapore, Singapore, Vagnas, France**

URLI (LY900014), a novel ultra-rapid mealtime insulin in Phase 3 development, is shown to reduce postprandial glucose after subcutaneous injection. This 2-part, randomized, double-blind, Phase 1b study evaluated the differences in PK and PD between URLI and insulin lispro (Humalog®; HL) in 30 patients with T1D. Part A used a 6-period crossover design to evaluate safety and compare PK and postprandial glucose response to solid mixed meal tolerance tests (MMTT) with URLI or HL at different injection to mealtime intervals (-15, 0 and +15 min). Part B evaluated the safety, PK, and PD during 2 weeks of multiple daily dosing (immediately before a meal) in a parallel design. In Part A, URLI reduced glucose excursions (assessed as change in area under the concentration curve vs. time [AUC]) during the first 2 hours (AUC0-2h) and entire 5 hours (AUC0-5h) of the MMTT regardless of dose timing (Fig). URLI reduced AUC0-2h by 103% (p<0.0001), 105% (p=0.001), and 28% (p=0.076) vs. HL at -15, 0 and +15 min (significance level =0.1). The PK and PD profiles for URLI and HL were sustained after 2 weeks of outpatient dosing (Part B). More hypoglycemic events occurred with URLI during MMTTs but these were mild and mostly asymptomatic. Only a few events occurred in either group during 2 weeks of outpatient dosing. Local tolerability was similar between treatments.
Human Regular U-500 Insulin via Continuous Subcutaneous Insulin Infusion vs. Multiple Daily Injections in Adults with T2D—The VIVID Study, Primary Population

GEORGE GRUNBERGER, ANUJ BHARGAVA, TRANG T. LY, HOWARD ZISSER, LIZA ILAG, JAMES K. MALONE, SHUYU ZHANG, JENNIFAL JOHNSON, Bloomfield Hills, MI; West Des Moines, IA; Billericia, MA; Santa Barbara, CA; Indianapolis, IN

VIVID is the first prospective, randomized controlled trial to assess efficacy and safety of U-500R (Humulin® R U-500) administered by CSII (using an investigational Omnipod U-500™ Insulin Management System) vs. MDI (TID). This 26-week, open-label, multicenter, parallel study (NCT02561078) enrolled adults with T2D on 201-600 units of insulin/day with or without other antihyperglycemic agents. We report data for the primary population (N=400), excluding participants on concomitant GLP-1 RAs or SGLT2 inhibitors. Data for the all-randomized population are reported separately. Baseline characteristics were similar between arms. CSII showed noninferior A1C reduction vs. MDI (primary objective) and superior FPG reduction at 26 weeks with adjustment for multiplicity. CSII showed significantly greater A1C reduction at a lower total daily dose with no multiplicity adjustment. Clinically important hypoglycemia rates (<54 mg/dL) and weight gain were similar; severe and nocturnal (<70 mg/dL) hypoglycemia rates were statistically higher for CSII vs. MDI (Table). In this population, U-500R via CSII had greater efficacy at a lower dose vs. MDI with higher hypoglycemia rates for some categories. CSII with U-500R may be a viable option for T2D patients on high-dose insulin. Individualized dose titration will be important to safely achieve A1C targets.

<table>
<thead>
<tr>
<th>Table.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome Measure</td>
</tr>
<tr>
<td>A1C (%)</td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Change</td>
</tr>
<tr>
<td>Difference (95% CI)</td>
</tr>
<tr>
<td>A1C &lt;7%</td>
</tr>
<tr>
<td>Endpoint, n(%)</td>
</tr>
<tr>
<td>A1C &lt;6.5%</td>
</tr>
<tr>
<td>Endpoint, n(%)</td>
</tr>
<tr>
<td>A1C &lt;6%</td>
</tr>
<tr>
<td>Endpoint, n(%)</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Change</td>
</tr>
<tr>
<td>TDD (units/kg)</td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Change</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Change</td>
</tr>
</tbody>
</table>

**Supported By:** Eli Lilly and Company

Continous Glucose Monitoring Guided Assessment of Concentrated U200 r-DNA Human Premix 30/70 Insulin

HEMANT THACKER, JOTHYDEV KESAVEDEV, GURSIMRAN SINGH, KIRTI SHUKLA, GAURAV PUPPALWAR, RUPAL SHRIMANKER, Mumbai, India; Trivandrum, India

Objective: With increasing longevity, obesity and late insulin initiation being common in type 2 diabetes mellitus (T2DM), concentrated insulin formulations could evolve as a choice in a subgroup of these subjects. Globally, 30% of T2DM use more than 60 units of insulin daily. U200 (r-DNA Human Insulin Premix 30/70 200IU/mL) insulin has been developed to provide sustained glucose-lowering effect and enhanced compliance without increasing the risk of hypoglycaemia. This study was conducted to assess the efficacy and safety of U200 insulin in terms of 24-hour glucose profiling using Continuous Glucose Monitoring (CGM) in T2DM.

Methods: Prospective, single-arm, open-label, multi-centre study evaluating glycaemic profile in 60 adults with T2DM administered with U200 was undertaken using CGM (iPro2, Medtronic USA) for 7 days. The endpoints assessed were time spent within acceptable glycaemic range, mean amplitude of glucose excursions (MAGE), and the duration and frequency of hyperglycaemic/hypoglycaemic periods.

Results: Mean age of subjects was 55.47 ± 9.68 (26-70) years. Mean blood glucose level was 151±23.93 (105.73-231.69) mg/dl. Blood glucose levels were within the normal limits (70-150 mg/dL) for 62.35% of time. Average numbers of hyperglycaemic and hypoglycaemic episodes observed were 2.64 and 0.22 with mean duration of 165.16 and 27.35 minutes respectively. MAGE was 77.24±22.50 (37.47-153.00) mg/dl. Medication adherence rate was 100% with no adverse event other than minor hypoglycemia reported.

Discussion and Conclusion: CGM provides 24-hour profiling of glycaemic metabolic control and identifies fluctuations. U200 premixed insulin demonstrated low intraday variability as measured by MAGE of 77.24 mg/dl and patients spending 62.35% of time within normal glucose limits, allowing for a more constant action with less frequent hypoglycaemic or hyperglycaemic excursions. U200 human premix insulin is effective, safe and well tolerated in T2DM patients.

**Supported By:** Wockhardt Ltd
Clinical Diabetes/Therapeutics

POSTERS

ADA-Supported Research

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—INSULINS

1014-P

Switching to Insulin Degludec from Insulin Glargine U100 Improves Glycemic Control in People with Type 1 (T1D) or Type 2 diabetes (T2D) in a Real-World Setting

SOREN T. KNUDSEN, NIKOLAOS TENTOLOURIS, BERND SCHULTES, ANNUNZIATA LAPOLLA, MARKUS EIDENMUeller, RUDOLF PRAGER, ANDREI-MIRCEA CATARlig, MICHAEL L. WOLKEN, THORSTEN SIEGMUND, Aarhus, Denmark, Athens, Greece, St. Gallen, Switzerland, Padova, Italy, Marburg, Germany, Vienna, Austria, Copenhagen, Denmark, Søborg, Denmark, Munich, Germany

EU-TREAT (NCT02662114), a European, multicenter, retrospective chart review study investigated the clinical impact of switching from any basal insulin to insulin degludec (degludec). This analysis aimed to evaluate the effectiveness of degludec after switching from insulin glargine 100 units/mL (glargine U100), under routine care. Patients with T1D or T2D were switched, based on clinical judgement, from glargine U100 to degludec at least 6 months before data collection. Baseline was defined as the most recent recording during the 3-months pre-switch period. Outcome data were collected at 6 ± 3 months and at 12 ± 3 months pre- and post-switch. Both HbA₁c and fasting plasma glucose (FPG) decreased significantly in patients with T1D (n=889) or T2D (n=259) at 6- and 12-months post-switch vs. pre-switch (all p<0.001, except for FPG at 12-months post-switch in T2D, p=0.023). Daily insulin dose decreased significantly in patients with T1D at 6- and 12-months post-switch vs. pre-switch (both p<0.001), but remained unchanged in patients with T2D. Hypoglycemia was significantly lower (all p<0.05) post-switch vs. pre-switch (Figure). Switching to degludec from glargine U100 significantly reduces HbA₁c, and risk of hypoglycemia under routine care.

Figure. Hypoglycaemia rate ratios for patients with T1D or T2D post- versus pre-switch

<table>
<thead>
<tr>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1D</td>
<td></td>
</tr>
<tr>
<td>Overall hypoglycaemia</td>
<td>0.73 (0.63; 0.84)</td>
</tr>
<tr>
<td>Non-severe nocturnal hypoglycaemia</td>
<td>0.57 (0.44; 0.73)</td>
</tr>
<tr>
<td>Severe hypoglycaemia</td>
<td>0.53 (0.38; 0.73)</td>
</tr>
<tr>
<td>T2D</td>
<td></td>
</tr>
<tr>
<td>Overall hypoglycaemia</td>
<td>0.21 (0.11; 0.38)</td>
</tr>
<tr>
<td>Non-severe nocturnal hypoglycaemia</td>
<td>0.49 (0.30; 0.78)</td>
</tr>
<tr>
<td>Severe hypoglycaemia</td>
<td>0.04 (0.01; 0.16)</td>
</tr>
</tbody>
</table>

Hypoglycaemia: overall (recorded by the physician/nurse), non-severe nocturnal (non-severe episodes captured by the words ‘nocturnal’, ‘night’ or their equivalent in the report) or severe (requiring the assistance of another person). CI, confidence interval; T1D, type 1 diabetes; T2D, type 2 diabetes

Supported By: Novo Nordisk A/S

1016-P

WITHDRAWN

1015-P

WITHDRAWN

1017-P

Improved Time-in-Range (TIR) on Continuous Glucose Monitor (CGM) with Technosphere Inhaled Insulin (TI) Compared with Insulin Aspart in T1D Patients—STAT Study

JANET K. SNELL-BERGEON, HAUS K. AKTURK, AMANDA REWERS, BRUCE W. BODE, LESLIE J. KLAFF, ANNE PETERS, TIMOTHY S. BAILEY, SATISH K. GARG, Aurora, CO, Denver, CO, Atlanta, GA, Renton, WA, Los Angeles, CA, Escondido, CA

Sixty patients with T1D on multiple daily injections (MDI) were randomized in a multi-center study, stratified by A1c values (<8.5% or ≥8.5%) to the control arm using aspart (n=34) vs. TI group (n=26). Patients in the TI arm were advised to take extra inhalations at 1 and 2 hours after meals based on post-prandial blood glucose (PPBG) values. Baseline characteristics and FEVI were similar. Using per protocol (PPT) analysis, we examined outcomes over the 4-week period using linear regression with repeated measures. The primary outcomes were TIR (70-180 mg/dL) and PPBG excursions.
Compliance with T1 was based on its use when indicated at 1- and 2-hour PPBG. Patients with at least 80% compliance were included in PPT (n=15). Seven T1 patients were non-compliant; 2 dropped out of the study; and 2 did not have CGM data.

CGM glucose patterns and TIR for a patient with 100% or with 56% compliance with T1 are shown (Figures 1a and 1b). TIR was significantly higher in the T1-compliant group compared to control or T1-non-compliant groups (Figure 1c). PPBG was also significantly lower in the T1-compliant compared to the control group at 1- and 2-hours post-prandial but not at 3 and 4 hours. PPBG was significantly lower in the compliant vs. non-compliant T1 group at all time points (Figure 1d).

We conclude that T1 improves TIR and PPBG values, if patients use additional inhalations as directed.

Figures 1a-1d.

Supported By: ManKind Corporation

Is It Possible to Predict the Onset of Nocturnal Severe Asymptomatic Hypoglycemia Using CGM Data of Previous Day and Next Morning in Type 1 Diabetic Patients Receiving Insulin Degludec?

HIROSHI TAKAHASHI, RIMI NISHIMURA, KAZUNORI UTSUNOMIYA, Tokyo, Japan

The aim of this study was to investigate whether the occurrence of nocturnal severe asymptomatic hypoglycemia (NH) may be predicted based on glycemic variability on the previous day and next morning the day on the onset. This study examined patients with type 1 diabetes (T1D) who underwent CGM assessments and received basal bolus therapy of insulin degludec (IDeg) in outpatient setting. NH was defined as glucose levels < 54 mg/dL detected between 12:00 and 6:00 AM. The subjects were evaluated for fasting glucose level, the range of post-breakfast glucose elevation, and glucose level at bedtime (12:00 AM) on the previous day. For comparison, the patients were divided into those with NH and those without by using t-test. Optimal cut-off values for the relevant parameters were determined in order to predict NH using ROC analysis. Thirty-one patients (mean HbA1c values, 7.8 ± 0.7%) were selected for analysis. NH occurred in 8 patients (26%). Fasting glucose level was significantly lower in those with NH than in those without (61 ± 13 mg/dL vs. 130 ± 68 mg/dL; P = 0.001). The range of post-breakfast glucose elevation was significantly greater in those with NH. Again, the glucose level at bedtime was significantly lower in those with NH than in those without (88 ± 44 mg/dL vs. 144 ± 69 mg/dL; P = 0.044). The cut-off values for predicting NH determined for the relevant factors were as follows: fasting glucose level < 69 mg/dL (sensitivity 0.83/ specificity 0.75/ AUC 0.86, P = 0.005) and bedtime glucose level < 90 mg/dL (0.83/0.75/0.79, P = 0.017).

The results suggest that fasting glucose level < 69 mg/dL and bedtime glucose level < 90 mg/dL had approximately 80% probability of predicting the occurrence of NH in T1D receiving IDeg. While the post-breakfast glucose levels and the pre- and post-dinner glucose levels were not significantly different, the range of post-breakfast glucose increase was greater in those with NH than in those without.

One-Year Safety and Effectiveness of Insulin Degludec in Patients with Diabetes Mellitus in Routine Clinical Practice in India—TRUST (Tresiba Real-World Use Study)

JUTHIDev KESAdev, L. SREenivasA MURTHY, SR., BANshi D. SABoo, SADASIVA RAO YALAMANCHI, BALAMURUGAN RAMANATHAN, SUnIL GUPTA, SANJAY CHATTERJEE, MANJUNATHA REVANNA, HARSHA KasetTY, Trivandrum, India, Bangalore, India, Ahmedabad, India, Vijayawada, India, Coimbatore, India, Nagpur, India, Kolkata, India

Insulin degludec (degludec) is a basal insulin with an ultra-long duration of action and low day-to-day variability in the glucose-lowering effect. The aim of this non-interventional, multicentric, prospective, post-authorization safety study (PASS) was to evaluate the long-term (1 year) safety and effectiveness of insulin degludec in patients with diabetes mellitus (DM) requiring insulin therapy on routine clinical practice conditions, as required by the Indian regulatory authority. Eligible patients who were started with degludec treatment as per the physician’s discretion were followed up and data was collected at baseline (BL), 3, 6 and 12 months in the time periods after degludec initiation. Values are expressed as mean(SD). A total of 1,057 adult patients with DM (5 with T1D and 1052 with T2D) were included. In total, 59.6% were male, mean age 55.9 (11.5) years, duration of diabetes 11.4 (7.6) years, body weight 71.6 (13.7) kg and HbA1c 9.5 (1.9)%.

Majority of the subjects (81.83%) were insulin-naïve at BL. At 12 months follow-up, 44 adverse events (AEs) were reported in 2.6% of the subjects and 2 AEs were serious. HbA1c decreased significantly compared to BL by 1.8% (1.68) (P<0.0001). Daily degludec dose increased from a starting dose of 14.8 (8.0) U to 18.01 (9.45) U and body weight increased from 71.68 (13.43) kg (BL) to 72.24 (12.88) kg. Hypoglycemia was reported in 5% of the subjects (85 events/100PYE) during the 12 months treatment period. The two most common reasons for prescribing degludec were to improve HbA1c (83.8%) and for control of fasting glucose (63.7%).

In conclusion, this PASS confirms the long-term safety of treatment with degludec with improvement in glycemic control and low risk of hypoglycemia in patients with T2D on routine clinical care.
The study suggests that U-500R is commonly used as insulin monotherapy. The observed adherence/persistence could be the result of the simplicity of U-500R regimen, which might benefit high-dose insulin-treated patients.

1022-P

Basal Insulin in Clinical Practice—Can Virtual Patient Simulation Improve Use in T2D?

AMY LARKIN, MICHAEL LACDUCITRE, MARTIN WARTERS, GWEN S. LITTMAN, New York, NY; Durham, NC

We sought to determine if online, virtual patient simulation (VPS)-based continuing medical education (CME) intervention could improve performance of primary care physicians (PCPs) and diabetologists/endocrinologists (D/Es) in evidence-based use of basal insulin for T2D. The intervention comprised two patients presenting in a VPS platform that allows learners to order lab tests, make diagnoses, and prescribe treatments in a manner matching the scope and depth of actual practice. Tailored clinical guidance (CG), based on current evidence and expert recommendation, was provided following each decision, followed by the opportunity to modify to their decisions. Decisions were collected post-CG and compared with each user’s baseline (pre-CG) decisions using a 2-tailed paired t-test to determine P values.

Significant improvements were observed after CG. Case 1 (n=477 PCPs; n=100 D/Es): Appropriate basal insulin initiation: 44% absolute improvement among PCPs (24% pre-CG vs. 68% post-CG; P<.001), 50% improvement among D/Es (30% pre-CG vs. 80% post-CG; P<.001) Order diabetes self-management education (DSME) in newly diagnosed patient: 19% absolute improvement among PCPs (50% pre-CG vs. 69% post-CG; P=0.014), 4% improvement among D/Es (59% pre-CG vs. 73% post-CG; P=.017) Titration plan: 27% improvement among PCPs (28% pre-CG vs. 55% post-CG; P<.001), 26% absolute improvement among D/Es (29% pre-CG vs. 55% post-CG; P<.001).

Case 2 (n=537 PCPs, n=132 D/Es): Selection of longer-acting basal insulin in T2D patient complaining of hypoglycemia: 34% absolute improvement among PCPs (31% pre-CG vs. 65% post-CG; P<.001), 39% improvement among D/Es (34% pre-CG vs. 55% post-CG; P<.001). Case 2 (n=447 continued U-500R beyond two years. Use beyond one year, 286 patients discontinued U-500R in the second year index to U-500R restart was 135 days. Out of the 733 patients with U-500R (70.9%) of patients resumed U-500R. The median time from end of post-index to U-500R restart was 135 days. Out of the 733 patients with U-500R use beyond one year, 286 patients discontinued U-500R in the second year and 447 continued U-500R beyond two years.

Supported By: Sanofi Aventis Deutschland GmbH
Lower Day-to-Day Fasting Self-Measured Plasma Glucose (SMPG) Variability with Insulin Degludec/Liraglutide (IDegLira) vs. Insulin Glargine 100 Units/mL (IGlar U100)

IUDIKI LINGYAR, ANIKUR DUSHI, PEDRO A. GARCIA-HERNANDEZ, JUAN FRANCISCO MERINO TORRES, MELANIE ROJACX, SARAH EGGERT, RANDI GRINN, ELMAR JACKEL, DALLAS, TX; HOUSTON, TX; MONTERREY, MEXICO; VALENCIA, SPAIN; RIO DE JANEIRO, BRAZIL; SEBOG, DENMARK; HANNOVER, GERMANY

Diabetes therapy aims for stable glycemic control and minimal hypoglycemia risk, previously linked to day-to-day variability. In a post hoc analysis, day-to-day fasting glycemic variability with IDegLira was compared with IGlar U100, in DUAL V (IDegLira vs. IGlar U100) and VII (IDegLira vs. IGlar U100 and bolus insulin aspart) respectively. Statistical analysis of weekly Variables showed a 32% (p<0.0001) and 23% (p=0.001) lower day-to-day fasting glycemic variability. Based on fasting SMPG values, there was lower day-to-day variability with IDegLira, possibly contributing to the lower hypoglycemia risk, compared with IGlar U100 in DUAL V and VII.

Table: Patients grouped according to tertiles of overall day-to-day SMPG variability by treatment

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Low variability</th>
<th>Medium variability</th>
<th>High variability</th>
<th>Probability of subjects having lower variability</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDegLira, DUAL V</td>
<td>38.1 ± 0.40</td>
<td>38.5 ± 1.61</td>
<td>23.0 ± 6.47</td>
<td>1.99 (1.46; 2.72)</td>
</tr>
<tr>
<td>IGlar U100, DUAL V</td>
<td>28.3 ± 0.75</td>
<td>28.3 ± 1.99</td>
<td>43.4 ± 9.95</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>IDegLira, DUAL VII</td>
<td>36.5 ± 0.23</td>
<td>35.7 ± 0.94</td>
<td>27.0 ± 2.45</td>
<td>1.55 (1.12; 2.14)</td>
</tr>
<tr>
<td>IGlar U100 +Asp, DUAL VII</td>
<td>29.1 ± 0.35</td>
<td>30.7 ± 5.49</td>
<td>36.8 ± 16.18</td>
<td>0.0085</td>
</tr>
</tbody>
</table>

Variability data are based on the FAS, hypoglycemia data are based on the SAS. Daily fasting SMPG values were used to calculate a weekly measure of day-to-day fasting glycemic variability measurement for each patient by calculating the variance of the daily log-transformed SMPG value. These weekly Variables were analyzed on log-scale in an ANCOVA model, with treatment as a factor, baseline fasting plasma glucose as a covariate and subject as a random effect. The standard deviation (square root of the mean of the weekly Variables) then produced an overall day-to-day fasting glycemic Variability measure for each subject, used to divide the entire study populations into tertiles. Hypoglycemia was defined as subject unable to treat himself/herself and/or have a recorded PO<0 mL for 1 min (0.1 mmol/L) in DUAL VII. The patients also had to have symptoms consistent with hypoglycemia.

OPA is based on modeling the probability of being in a lower variability group. Overall day-to-day variability group (High, Medium, Low) is analyzed in multinomial model using a cumulative logit link function. The model includes treatment as a fixed factor.

Supported By: Adocia

Reasons for Discontinuation of Insulin Therapy—Results from the International Diabetes Management Practices Study (IDMPS)

PABLO ASCHNER, JUAN J. GAGLIARDINO, HASAN M. ILKOVA, FERNANDO J. LAVALLÉE-GONZALEZ, SR., AMBADDY RAMACHANDRAN, GAHIDA KADDAHA, JEAN-CLAUDE MBANYA, MARINA V. SHESTAKOVA, JEAN-MARC CHANTELOT, JULIANA C. CHAN, Bogotá, Colombia; La Plata, Argentina; Istanbul, Turkey; Monterrey, Mexico; Chennai, India; Dubai, United Arab Emirates; Yaoundé, Cameroon; Moscow, Russian Federation; Paris, France; Hong Kong, China

Adherence to insulin therapy is often suboptimal. Understanding patients’ perspectives on drug adherence is essential for identification of barriers to therapy. The IDMPS is a global observational survey on the management...
of people with type 1 (T1D) and type 2 T2D) diabetes in the developing world. In 2016-2017, participants were enrolled from 24 countries in the Middle East, South Asia, Eurasia, and Africa. In people with T1D (N=2000), 14% (273/1955) discontinued insulin for 1 month (median), without physician indication. The main reasons given were impact on social life, cost, fear of hypoglycemia, and lack of support (Table 1).

In people with T2D (N=2956), insulin discontinuation for ≥2 months (median), without physician indication, was reported by 13.4% and 13.8% of people treated with insulin alone (n=642) or with an oral antihyperglycemic drug + insulin (n=1895), respectively. The most common reasons for discontinuation included impact on social life, fear of hypoglycemia, lack of support, and cost. The pattern of insulin (e.g., a definitive or temporary stop, or missed injection(s)) was not documented.

People with T1D and T2D share similar concerns regarding therapy. This calls for a multi-pronged strategy including patient education and access to therapy to improve treatment adherence and optimize outcomes.

Supported By: Sanofi

**1027-P**

Initiating Basal Insulin Supported Oral Therapy (BOT) with Insulin Glargine 300 U/mL (Gla-300) Improves Glycemic Control in Patients (Pts) with Type 2 Diabetes (T2DM) without Increasing Hypoglycemia Risk

MARTIN PFÖHL, ANDREAS FRITSCHE, HELMUT ANDERTEN, KATRIN PEGELOW, STEFAN PSCHERER, JOCHEN SEUFERT, DUIBRS, Germany, TÜBINGEN, Germany

Toopé-J, a prospective observational study, investigates the effects of initiating BOT with Gla-300 in insulin-naïve pts with T2DM in Germany, Hildesheim, STUFEN PSCHERER, JOCHEN SEUFERT, DUIBRS, Germany, MAARTIN PFOHL, ANDREAS FRITSCHE, HELMUT ANDERTEN, KATRIN PEGELOW.

**Table 1: Reasons for insulin discontinuation**

<table>
<thead>
<tr>
<th>Reason for discontinuation (%)</th>
<th>T2D</th>
<th>T2D</th>
<th>T2D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of efficacy</td>
<td>3.3</td>
<td>5.8</td>
<td>9.2</td>
</tr>
<tr>
<td>Fear of hypoglycemia</td>
<td>26.7</td>
<td>24.4</td>
<td>29.1</td>
</tr>
<tr>
<td>Occurrence of side effects</td>
<td>8.4</td>
<td>12.8</td>
<td>10.3</td>
</tr>
<tr>
<td>Impact on social life</td>
<td>41.0</td>
<td>29.1</td>
<td>31.0</td>
</tr>
<tr>
<td>Lack of experience in insulin dosing</td>
<td>20.9</td>
<td>30.2</td>
<td>24.1</td>
</tr>
<tr>
<td>Lack of experience in insulin administration</td>
<td>9.5</td>
<td>16.3</td>
<td>14.2</td>
</tr>
<tr>
<td>Cost of medicine and strips</td>
<td>34.4</td>
<td>22.1</td>
<td>25.3</td>
</tr>
<tr>
<td>Weight gain</td>
<td>8.8</td>
<td>4.7</td>
<td>10.3</td>
</tr>
<tr>
<td>Lack of support</td>
<td>26.4</td>
<td>29.1</td>
<td>24.9</td>
</tr>
<tr>
<td>Occurrence of hypoglycemia</td>
<td>14.7</td>
<td>15.1</td>
<td>11.9</td>
</tr>
</tbody>
</table>

OGIWL, oral glucose-lowering drug.

Supported By: Sanofi Aventis Deutschland GmbH

**1028-P**

Self-Managed Titration with Insulin Glargine 300 U/mL (Gla-300) Can Achieve Similar Efficacy to Physician-Led Titration Regardless of Prior Insulin Status in People with T2DM—Results from TAKE CONTROL

ELIAS DELGADO, MIREILLE BONNEMAIRE, ARNAUD DAUCHY, VIERA DONICOUVA, MILAN KAVPIL, NIKOLAOS TENTOLOURIS, LUZIA POPESCU, DAVID RUSSELL-JONES, Oviedo, Spain; Paris, France; Kosice, Slovakia, Prague, Czech Republic, Athens, Greece, Bucharest, Romania, Guildford, United Kingdom

Many people with T2DM do not achieve HbA1c goals in clinical practice, owing in part to sub-optimal basal insulin titration. TAKE CONTROL, a 24-week, multicenter, randomized, open-label, parallel-group study, compared the efficacy and safety of a Gla-300 titration algorithm (fasting self-monitored plasma glucose ≥70 mg/dL or <54 mg/dL, ±3 U; <30 mg/dL, ±3 U) to self-titration. Here, we report results stratified by prior insulin use. At baseline, mean HbA1c was higher in the insulin-naïve vs. prior-insulin group (Table). In both groups, self-titration with reduced or similar risk of hypoglycemia. Empowering people with T2DM to self-titrate their basal insulin effectively upon Gla-300 initiation, or after switching to Gla-300, can improve glycemic target achievement without increasing hypoglycemia.
Impact of Background Antihyperglycemic Therapy on Insulin Glargine 300 U/mL (Gla-300) vs. Insulin Degludec 100 U/mL (IDeg-100) in Insulin-Naive People with T2DM from the BRIGHT Randomized Study

RONAN RÖUSSEL, JULIO ROSENSTOCK, JEREMY PETTUS, ROBERT RITZEL, ALICE CHENG, ZSOLT BOSNYAK, CHRISTINE DEVISME, ANNA M. CALI, XIANG-LING WANG, GEREMIA B. BOLLI, RONAN ROUSSEL, JULIO ROSENSTOCK, JEREMY PETTUS, ROBERT RITZEL, CLINICAL THERAPEUTICS/NEW TECHNOLOGY—INSULINS

BRIGHT (NCT02738151), the first head-to-head trial of Gla-300 and IDeg-100 in T2DM, is a multicenter, open-label, randomized, parallel-group, 24-week actively controlled study, conducted in insulin-naive participants uncontrolled on current antihyperglycemic drugs. Participants (mean baseline HbA1c 8.6%, diabetes duration 10.6 years, BMI 31.5 kg/m²) received Gla-300 (N=466) or IDeg-100 (N=463), titrated to a fasting SMPG of 80-100 mg/dL, and remained on metformin ± previous antihyperglycemic therapy. Participants were enrolled from 24 countries in the Middle East including Pakistan, South Asia (India, Bangladesh), Eurasia (Russia, Ukraine) and Africa in 2016-17. Physicians reported the challenges their patients face in achieving glycemic goals.

In conclusion, background antihyperglycemic therapies had no impact on glycemic control in T1D and T2D. Factors related to discontinuation of insulin, lack of support, and insufficient knowledge are major barriers to glycemic control in T1D and T2D. Factors related to hypoglycemia are more common in T1D. These data highlight the need for appropriate education strategies and sustained access to therapy.

Table 1. Physician-reported reasons for non-achievement of glycemic target in people with T1D and T2D

<table>
<thead>
<tr>
<th>Reason</th>
<th>T1D</th>
<th>T2D</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation of insulin</td>
<td>11.5</td>
<td>10.2</td>
<td>9.9</td>
</tr>
<tr>
<td>Lack of support</td>
<td>19.3</td>
<td>22.7</td>
<td>21.1</td>
</tr>
<tr>
<td>Lack of diabetes education</td>
<td>28.4</td>
<td>35.0</td>
<td>35.0</td>
</tr>
<tr>
<td>Lack of tectomy of insulin</td>
<td>38.9</td>
<td>40.8</td>
<td>39.3</td>
</tr>
<tr>
<td>Lack of experience in insulin dosing</td>
<td>29.3</td>
<td>40.1</td>
<td>34.5</td>
</tr>
<tr>
<td>Cost of medicine and strips</td>
<td>30.2</td>
<td>32.9</td>
<td>26.2</td>
</tr>
<tr>
<td>Weight gain</td>
<td>12.5</td>
<td>17.9</td>
<td>20.7</td>
</tr>
<tr>
<td>Fear of hypoglycemia</td>
<td>40.8</td>
<td>26.2</td>
<td>25.1</td>
</tr>
<tr>
<td>Occurrence of hypoglycemia</td>
<td>22.1</td>
<td>13.7</td>
<td>6.5</td>
</tr>
</tbody>
</table>

OGDL, oral glucose-lowering drug.

Supported By: Sanofi

Clinical Diabetes/Therapeutics POSTERS
Comparison of Different Self-Adjustment Regimens of Basal Insulin in Outpatients with T2DM

XILING HU, XUBIN YANG, WEN XU, HONG R. DENG, XIAXO GUO, BIN YAO, LONGYI ZENG, JIANPING WENG, Guangzhou, China

Self-adjustment of basal insulin dose were proved to be effective and widely used in clinical practice. However, no study compares the efficacy and safety of different self-adjustment regimens of basal insulin in T2DM.

T2DM with inadequate glucose control on OADs who were to start basal insulin from our outpatient clinics were enrolled and randomized to two groups. Patients in Group A were guided to adjust insulin dose 2-6U weekly; those in Group B adjusted insulin dose 2-3U every 3 days. Dose titration was based on self-monitored blood glucose (SMBG) to achieve a target FBG of 6.1mmol/L. The titration regimen is shown in Table.
Clinical Diabetes/Therapeutics

Moderated Poster Discussion

Clinical Theraeutics/New Technology—Insulins

1034-P

WITHDRAWN

1035-P

The Ultra-Rapid Insulin (URI) BioChaperone Lispro (BCLIS) Shows Favorable Pharmacodynamics (PD) and Pharmacokinetics (PK) vs. Faster Aspart (FIA) and Insulin Aspart (ASP) in Insulin Pumps (CSII)

BRUCE W. BODE, OLIVER KLEIN, CYRIL SEROUSSI, AMERIC RANSON, JORGE ARRUBILA, JOSÉ CORREA, MARTIN GAUDIER, OLIVIER SOULA, REMI SOULA, BERTRAND ALLUIS, GREGORY MEIFFREN, STANISLAV GLEZER, TIM HEISE, 

Atlanta, GA; Neuss, Germany; Lyon, France; Skillman, NJ

This double-blind randomized crossover trial is the first to compare the PD and PK properties of two URIs (BCLIS and FIA) and of a conventional analog (ASP). Forty-three patients with type 1 diabetes received a bolus of 0.15 U/kg of BCLIS, FIA or ASP with CSII on top of a 0.01 U/kg/h basal rate under euglycemic clamp conditions (ClampArt®). Compared to ASP, BCLIS had significantly faster-on and -off PD with higher AUCs in the first two hours, lower AUCINS 0-1h and earlier tlate0.5INSmax and tlate0.5GIRmax (Table, Figure). Compared to FIA, BCLIS showed similar early GIR excursions and a significantly faster-off PD with earlier tlate0.5GIRmax. PK was aligned with PD and showed higher early (0-1h) and lower late (2-6h) exposures of BCLIS vs. FIA.

Table. Means SD PD and PK Parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>BCLIS</th>
<th>ASP</th>
<th>FIA</th>
<th>p-value BCLIS/ASP</th>
<th>p-value BCLIS/FIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUCGIR 0-2h [mg/kg]</td>
<td>PD effect in first two hours</td>
<td>596±276</td>
<td>504±244</td>
<td>582±276</td>
<td>0.0008</td>
<td>0.1277</td>
</tr>
<tr>
<td>AUCGIR 2-6h [mg/kg]</td>
<td>PD effect 2-6 hours post-dose</td>
<td>998±387</td>
<td>936±288</td>
<td>1053±288</td>
<td>0.0015</td>
<td>0.0097</td>
</tr>
<tr>
<td>tearly0.5GIRmax [min]</td>
<td>Time to early half-maximum PD</td>
<td>46±22</td>
<td>57±19</td>
<td>42±13</td>
<td>&lt;0.0001</td>
<td>0.9203</td>
</tr>
<tr>
<td>tlate0.5GIRmax [min]</td>
<td>Time to late half-maximum PD</td>
<td>210±88</td>
<td>232±52</td>
<td>226±61</td>
<td>0.0020</td>
<td>0.0017</td>
</tr>
<tr>
<td>AUCINS 0-1h [h.mU/L]</td>
<td>Insulin exposure 0-1 hour post-dose</td>
<td>66±27</td>
<td>49±22</td>
<td>59±21</td>
<td>&lt;0.0001</td>
<td>0.0284</td>
</tr>
<tr>
<td>AUCINS 2-6h [h.mU/L]</td>
<td>Insulin exposure 2-6 hours post-dose</td>
<td>81±43</td>
<td>95±41</td>
<td>93±45</td>
<td>0.0006</td>
<td>0.0001</td>
</tr>
<tr>
<td>tlate0.5INSmax [min]</td>
<td>Time to late half-maximum insulin concentrations</td>
<td>140±48</td>
<td>183±68</td>
<td>195±59</td>
<td>&lt;0.0001</td>
<td>0.0028</td>
</tr>
</tbody>
</table>

WITHDRAWN

1036-P

Similar Variability of Fasting and 24-h Self-Measured Plasma Glucose (SMPG) with Insulin Glargine 300 U/mL (Gla-300) vs. Insulin Degludec 100 U/mL (Ideg-100) in Insulin-Naïve Adults with T2DM—The Randomized BRIGHT Trial

ALICE Y.Y. CHENG, ROBERT RITZEL, ZSOLT BOSNYAK, EMMANUELLE BOELE-LE CORFEC, ANNA M. CALI, XIANGLING WANG, JUAN P. FRIAS, RONAN ROUSSEL, GEREMIA B. BOLLI, MISSISSAUQA, ON, Canada, Munich, Germany, Paris, France, Chilly-Mazarin, France, Tokyo, Japan, Beijing, China, Los Angeles, CA, Perugia, Italy

BRIGHT was an open-label, randomized, parallel-group, 24-week study in insulin naïve participants with uncontrolled T2DM, investigating efficacy and safety of Gla-300 and Ideg-100. Participants were randomized to Gla-300 or Ideg-100, titrated to a target fasting SMPG of 80-100 mg/dL. The primary objective (non-inferiority of Gla-300 vs. Ideg-100 in HbA1c change from baseline to week 24) was met. Secondary endpoints, presented here, included change in variability of fasting and 24-h SMPG. Eight-point SMPG profiles were similar for both groups at week 24. Mean baseline coefficient of variation (CV) of ≥3 fasting SMPG measurements over 7 days was 13.73% and 14.63% for Gla-300 and Ideg-100, respectively. Change in fasting SMPG variability (SE) to week 24 was 1.49% (0.39) and 1.97% (0.39) for Gla-300 and Ideg-100 (least squares [LS] mean difference [95% CI] −0.48 [−1.49 to 0.53]) (Figure a). Mean baseline CVs for 8-point profiles (24-h SMPG) were 22.60% and 23.41% for Gla-300 and Ideg-100. Mean change in 24-h SMPG variability (SE) was 3.70% (0.59) and 3.95% (0.60) for Gla-300 and Ideg-100 at week 24 (LS mean difference −0.25 [−1.72 to 1.22]) (Figure b).

In summary, Gla-300 and Ideg-100 had similar variability of fasting and 24-hour SMPG over the 24-week treatment period in BRIGHT.

Supported By: Sanofi (NCT02738151)

Supported By: Adocia

Clinical Diabetes/Therapeutics

POSTERS

ADA-Supported Research

Moderated Poster Discussion

A273
1037-P
Change in Insulin Dose and HbA1c by Geographical Region—Results from the Diabetes Unmet Need with Basal Insulin Evaluation (DUNE) Study
DIDAC MAURICIO, LUIGI MENEGHINI, EMANUELA ORSI, VADIM KLIMONTOV, JUKKA WESTERBACKA, LYDIA MELAS-MELT, VALERIE PILORDET, RICCARDO PEFETTI, KAMELISH KHINTI, BADALONA, SPAIN; DALLAS, TX, Milan, Italy; Novosibirsk, Russian Federation; Paris, France; Leuvaillios-Pernet, France; Bridgewater, NJ, Leicester, United Kingdom

DUNE, a 12-week, prospective, observational study (February 2015–July 2016) of 3139 people with T2DM, either newly (at enrollment) or recently (<12 months, mean 5.7 months) initiated on basal insulin (BI), aimed to assess the impact of symptomatic hypoglycemia on individualized HbA1c target achievement. Only 27.3% and 26.8% of newly and recently initiated participants, respectively, achieved individualized HbA1c targets. This analysis investigated the regional variations in BI dose and HbA1c change from baseline, which may help characterize treatment practices associated with improved target achievement. Mean baseline daily BI dose across regions ranged from 0.14 to 0.21 U/kg for newly initiated and 0.25 to 0.39 U/kg for recently initiated participants. Mean baseline HbA1c ranged from 8.9 to 9.4% (newly initiated), and 9.3 to 9.7% (recently initiated) across regions. In general, HbA1c reductions were greater in newly vs. recently initiated participants, and accompanied by greater increases in daily insulin dose (Figure), except in Nordic Europe, where HbA1c reductions were similar despite a −3.0% difference between groups in BI dose increases from baseline. These results show that the relationship between BI dose increase and HbA1c reduction can be variable, potentially reflecting regional differences in practices or populations that warrant further analysis.

![Figure: Mean change in HbA1c over the study period by geographical region](image)

**Supported By:** Sanofi (OBS13780)

1038-P
Pharmacokinetics and Pharmacodynamics of Human Regular U-500 Insulin (U-500R) Administered via Continuous Subcutaneous Insulin Infusion (CSII) vs. Subcutaneous Injection (SCI) in Adults with Type 2 Diabetes and High Insulin Requirements
XIAOSI MA, RANDY P. PRESCILLA, SHUYU ZHANG, HELLE LINNEBERG, LINDA LEISHMAN, JEFFREY A. JACKSON, JENNAL JOHNSON, DEREK LEISHMAN, A274, Napopolis, IN, Chula Vista, CA

There have been no euglycemic clamp studies on U-500R in obese patients with type 2 diabetes mellitus (T2DM) and high insulin requirements. This open-label, randomized, 2-way crossover, euglycemic clamp study (NCT02588950) evaluated PK/PD of U-500R administered by CSII (using an investigational Omnipod® U-500 Insulin Management System) compared to SCI (using a U-100 syringe), in adults with T2DM requiring >750 U/day of insulin. Subjects (N=11, mean BMI: 39.6 kg/m², mean A1C: 10.2%), each received a 100 U dose via CSII (primed with a 12-hour (hour) U-500R basal infusion) and a single SCI, both followed by a 24 hour clamp. Serum insulin concentrations were corrected for endogenous insulin using C-peptide for both administration methods. Basal infusion values in CSII were adjusted to gate the regional variations in BI dose and HbA1c change from baseline, which may help characterize treatment practices associated with improved target achievement. Mean dose change in BI dose across regions ranged from 0.14 to 0.21 U/kg for newly initiated and 0.25 to 0.39 U/kg for recently initiated participants. After 12 weeks, mean 5.7 months) initiated on basal insulin (BI), aimed to assess the impact of symptomatic hypoglycemia on individualized HbA1c target achievement. Only 27.3% and 26.8% of newly and recently initiated participants, respectively, achieved individualized HbA1c targets. This analysis investigated the regional variations in BI dose and HbA1c change from baseline, which may help characterize treatment practices associated with improved target achievement. Mean baseline daily BI dose across regions ranged from 0.14 to 0.21 U/kg for newly initiated and 0.25 to 0.39 U/kg for recently initiated participants. Mean baseline HbA1c ranged from 8.9 to 9.4% (newly initiated), and 9.3 to 9.7% (recently initiated) across regions. In general, HbA1c reductions were greater in newly vs. recently initiated participants, and accompanied by greater increases in daily insulin dose (Figure), except in Nordic Europe, where HbA1c reductions were similar despite a −3.0% difference between groups in BI dose increases from baseline. These results show that the relationship between BI dose increase and HbA1c reduction can be variable, potentially reflecting regional differences in practices or populations that warrant further analysis.

![Figure: Mean change in HbA1c over the study period by geographical region](image)

**Supported By:** Sanofi (OBS13780)

1039-P
Achievement of Individualized HbA1c Targets with Self- vs. Physician-Led Titration of Basal Insulin (BI) in People with Type 2 Diabetes (T2DM), Newly or Recently Initiated on BI—Results from the DUNE Real-World Study
LIRI BERARD, DIDAC MAURICIO, KAMELISH KHINTI, DENISE R. FRANCO, JUKKA WESTERBACKA, CHRISTOPHE CANDELAS, VALERIE PILORDET, RICCARDO PEFETTI, LUIGI MENEGHINI, Winnipeg, MB, Canada; Badalona, Spain; Leicester, United Kingdom; São Paulo, Brazil; Paris, France; Chilly-Mazarin, France; Bridgewater, NJ, Dallas, TX

DUNE was a 12-week, prospective, observational study of 3139 adults with T2DM, newly (at enrollment) or recently (<12 months) initiated on BI. We evaluated the achievement of individualized HbA1c targets at 12 weeks according to self- vs. physician-led insulin titration. Irrespective of titration method, the proportion of participants who achieved their individualized HbA1c target at week 12 was ≤30% in both the newly- and recently-initiated BI groups (Table). For both titration groups, there were comparable improvements in fasting plasma glucose from baseline and similar incidence of hypoglycemia. Increase in total daily BI dose for self- vs. physician-led titration in the recently initiated BI group was 4.85 vs. 4.91 U, respectively, while in newly initiated individuals it was 9.68 vs. 7.71 U, respectively. Most participants who were self-titrating did so every 1-3 days, compared with no more than 0.5-1 times per week for most participants who had physician-led titration. In all groups, the most frequently utilized dose increment was 2 U. The inability to most participants of their target HbA1c in a real-world scenario, irrespective of the method of titration, warrants further investigation.

**Table: Comparison of physician-led and self-titration in participants newly or recently initiated on BI.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Newly Initiated (n=2292)</th>
<th>Recently Initiated (n=847)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGI Target achievement (%)</td>
<td>30.8 (27.2)</td>
<td>20.5 (30.4)</td>
</tr>
<tr>
<td>CGI Change from baseline to week 12 (mg/dL)</td>
<td>5.40 (3.86)</td>
<td>7.05 (3.27)</td>
</tr>
<tr>
<td>BI dose change from baseline (U)</td>
<td>2.85 (1.46)</td>
<td>4.12 (2.36)</td>
</tr>
<tr>
<td>Area under the curve (AUC) (mg/dL)</td>
<td>22.3 (12.6)</td>
<td>14.5 (6.5)</td>
</tr>
</tbody>
</table>

**Supported By:** Sanofi (OBS13780)

1040-P
Short-Term Effects of Basal-Plus Insulin Therapy on Early Remission of Newly Diagnosed Type 2 Diabetes
EMMA WOKS, MARTINE CLAUDE ETNOGOU, RAICHA NAMBA, JEAN CLAUDE N’JABOU KATTE, JEAN CLAUDE MBANYA, EUGÈNE SOBNISWI, Yaoundé, Cameroon

Objective: Ketosis prone diabetes has been associated with prolonged normoglycemic remission after discontinuation of early intensive insulin therapy. However, it is unknown if such an approach can produce similar results in classical type 2 diabetes (T2DM). Therefore, our study sought to assess the effects of an outpatient regimen of basal-plus insulin therapy on early remission of newly diagnosed T2DM.

Research Methods: Newly diagnosed T2DM patients had an 8-week course of basal-plus insulin therapy which was then discontinued. Weekly 4-point glycemic profiles were done. HbA1c, lipid profile and insulin sensitivity, using the hyperinsulinenic euglycemic clamp were assessed at baseline and after the intervention. Early remission was defined as HbA1c <48 mmol/mol without treatment for at least 12 weeks.

Results: Eleven patients were included on diagnosis. Fasting blood glucose decreased (12.7 [7.8-15.0] vs. 4.9 [4.2-6.2] mmol/l). HbA1c dropped from 10.10 [8.0-10.8] to 42.0 [36.0-50.0] mmol/mol after basal-plus insulin therapy and was maintained at 38.0 [33.0-43.0] mmol/mol after 12 weeks with no
active treatment. Ten out of eleven subjects experienced early remission. Insulin sensitivity improved significantly after the intervention with a variation in the adjusted M-value from 7.95 [8.39-11.03] to 12.85 [10.24-14.92] mg/kg/min. The distinctive feature of those who did not require antidiabetic medications was that their initial standardized M-value was > 5.0 mg/kg/min. A significant decrease in total cholesterol and LDLc was observed from 5.40 [5.17-5.67] to 4.45 [3.57-5.48] mmol/L, and from 3.83 [2.82-4.37] to 1.06 [0.54-2.95] mmol/L, respectively. HDLc increased significantly from 1.14 [1.03-1.40] to 1.22 [1.18-2.89] mmol/L.

Conclusion: Basal-plus insulin therapy is effective, feasible, and safe in newly diagnosed T2DM and can induce early remission as observed in ketoacidosis prone diabetes.

Supported By: Recherche-santé et développement Hopit

1041-P

Efficacy and Safety of Biphasic Insulin Aspart Treatment in Hospitalized Patients with T2DM—A Real-World Study
RAVI S. ERUKULAPATI, APAWARA YERRAMILLI, VISHALAKSHI KANCHERLA, GOPALA RAO S. SREELALITHA, ANITHA POOLU, FATIMA Z. KHAN, KRISHNA REDDY CHAPPIDI, Hyderabad, India

Aim: To evaluate the efficacy and safety of biphasic insulin aspart during first 2 to 8 days of hospital admission of patients with type 2 diabetes (T2DM) for non-glycemia related medical ailments.

Methods: An open-label, non-randomized, observational, single-center study in patients with T2DM aged between 18 and 70 years at a tertiary multispecialty hospital in India. T2DM patients with capillary blood glucose (BG) between 70 mg/dl to 400 mg/dl at admission, requiring subcutaneous biphasic insulin aspart were included in this study. Insulin dosage was individualized as per the clinician’s judgement considering the clinical status, HbA1c and other co-morbidities. The primary endpoint was mean capillary BG levels at fasting, prandial, predinner and at midnight during day 2 to day 8 of hospital stay. Secondary endpoints were frequency and severity of hypoglycemic episodes. Appropriate statistics were applied at 2-tailed p≤0.05 significance.

Results: Total 205 T2DM patients were included in this study. Median age was 57 years, 66.3% male and 33.7% female. Mean duration of T2DM was 9.9 years, HbA1c 7.3%, BMI 25.9 kg/m2 and hospital stay 8.9 days. The mean (SD) BG at admission was 208.5 [82.9] mg/dL and after usage of Biphasic Insulin Aspart 188.2 [45.3] mg/dL. Mean capillary BG levels at fasting, prandial, predinner, and at midnight were 166.9 [46.7] mg/dL, 201.0 [58.8] mg/dL, 203.9 [60.1] mg/dL, and 179.0 [48.7] mg/dL, respectively. BG readings that met the target BG range (140-180 mg/dL) levels were 34.6%. During the study 5.9% of patient’s experienced hypoglycemic event of which 2% were severe requiring intravenous dextrose and 3.9% were mild. There was a significant difference in BG reduction correlating with BMI, HbA1c (p<0.05).

Conclusions: Treatment with biphasic insulin aspart is observed to be effective in achieving optimal BG levels, is well-tolerated with low hypoglycemic events in patients admitted in hospital for non-glycemia related medical ailments.

1042-P

Lower Pharmacokinetic and Pharmacodynamic Within-Day Variability of Individual Clinical Doses of Insulin Glargine 300 U/mL vs. Glargine 100 U/mL in T1DM
CARMINE FANELLI, PAOLA LUCIDI, PAOLA CANDELMERO, PATRIZIA CIOLU, ANNA MARINELLI ANDREOLI, SEREMIA B. BULLI, FRANCESCA PORCELLATI, Perugia, Italy

Previous studies have examined variability of pharmacokinetics (PK, plasma insulin concentration) and pharmacodynamics (PD, glucose infusion rate, GIR) of basal insulins at steady-state (SS) and at fixed doses in all subjects studied. To establish within-day PK/PD variability of individual, different, doses of insulin Glargine 300 U/mL (Gla-300) vs. Glargine 100 U/mL (Gla-100) that people with T1DM use in real life. Eighteen T1DMs [age 40±11 years, diabetes duration 26±12 years, BMI 23±4±1 kg/m2, A1C 7.2±0.5% (55±6 mmol/mol)] were studied after 3 month treatment with Gla-300 and Gla-100 titrated to fastening euglycemia, with a 24 h euglycemic clamp (randomized, crossover). The individual basal insulin doses that subjects used (0.35±0.08 Gla-300, 0.28±0.07 Gla-100, U/kg) were injected s.c. in the clamp study. Prior to clamp, glycemic control was comparable with Gla-300 and Gla-100. In the clamp, the individual doses of Gla-300 and Gla-100 resulted in 24 h PK/PD bioequivalence, but in lower variability indices of PK/PD with Gla-300 vs. Gla-100 (Table).

In conclusion, at clinical, individual doses used by T1DMs in real life, Gla-300 has lower PK/PD within-day variability vs. Gla-100. These results may explain the lower glycemic variability and lower risk for hypoglycaemia reported in clinical studies with Gla-300 vs. Gla-100.
The Characteristics of Patients with Long Remission after Short-Term Insulin Intensive Therapy

XUESI WANG, JUAN LIU, ZHIHUN HUANG, LIHUA LIU, YANBING LI, GUANGZHOU, China

In our previous study, some patients with newly diagnosed type 2 diabetes mellitus can maintain euglycaemia without hypoglycaemic agents after 2-week intensive insulin therapies for long time. But the others didn’t respond well to the treatment. To identify patients who would get long-remission from this treatment, a retrospective study was conducted to compared the characteristics between them. An observation of 160 patients with newly diagnosed T2DM patients aged 50±10 yrs by HbA1C >10% on average (94.8±8.8%) after 2-week therapy was studied remission rate. After the termination of short-term CSII, 65.6% patients maintained long-remission more than 1-year, 18.1% patients got remission less than 1-year, and 16.3% patients didn’t get remission from the therapy. Age, BMI and glucose metabolism at baseline were not significantly different among three groups. As the Table showed below, the long-remission patients have statistically lower FPG, PPG and better HOMA-B just after therapy.

In conclusion, the beta cell function (which test by HOMA-B) might affect the remission rate mainly by the better improved metabolism of glucose.

Table.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Coefficient</th>
<th>SE</th>
<th>Chi-square</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td></td>
<td>4.954</td>
<td>0.14</td>
<td>95.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>0.175</td>
<td>0.04</td>
<td>16.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes duration</td>
<td>years</td>
<td>-0.058</td>
<td>0.007</td>
<td>27.59</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline BMI</td>
<td>kg/m²</td>
<td>0.056</td>
<td>0.012</td>
<td>13.03</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>Baseline HbA1C</td>
<td>%</td>
<td>0.023</td>
<td>0.06</td>
<td>12.89</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>Baseline FPG</td>
<td>mg/dL</td>
<td>0.005</td>
<td>0.001</td>
<td>8.83</td>
<td>0.003</td>
</tr>
<tr>
<td>Baseline 2h PPG, overall</td>
<td>mg/dL</td>
<td>-0.054</td>
<td>0.002</td>
<td>13.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight change</td>
<td>kg</td>
<td>-0.062</td>
<td>0.03</td>
<td>21.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Overall hypoglycaemia</td>
<td>None</td>
<td>-0.223</td>
<td>0.04</td>
<td>27.16</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Mean (SD) or % people based on overall confirmed plasma glucose <3.9 mmol/L *Mean (SD), or as assistance required.

Supported By: Sanofi

Insulin Therapy in Type 3c Diabetes—More Common in Chronic Rather than Acute Pancreatitis

WILLIAM HINTON, MICHAEL FEHER, NEIL M. MUNRO, RACHEL M. COYLE, SIMON DE LUSIGNAN, Guilford, United Kingdom

Background and Aims: Prevalence of diabetes following pancreatic disease (Type 3c: diabetes— More Common in Chronic rather than Acute Pancreatitis (CP)) is common. Consequently, there is little real-world data on prescribing of anti-hyperglycaemic medications in people with T3cDM. The aim of this study is to evaluate prescribing of anti-hyperglycaemic medications in people with T3cDM.

Methods: A cohort of adults with a diagnosis of pancreatitis preceding diabetes, i.e., probable T3cDM, were identified from primary care records in England, the Royal College of General Practitioners Research and Surveillance Centre database (N = 1,595,445). The cohort was divided into those with acute (AP) or chronic pancreatitis (CP). People who presented initially with AP and subsequently developed CP were categorised as the latter. We performed retrospective analyses to compare the proportions of antihyperglycaemic medications prescribed in these subgroups. Chi square (K2) tests were used to test for differences between proportions.

Results: Of the 45,815 people living with diabetes, we identified 72% (1.6%) with pancreatitis preceding their diagnosis (AP = 456; CP = 29). The majority of those affected were prescribed noninsulin therapies (74.8%). Metformin was the most commonly prescribed medication (58.4%), followed by sulfonylureas (26.3%), insulin (25.2%) and DPP-4 inhibitors (13.6%). People with AP were more likely to be prescribed metformin (82.3% vs. 45.0%; p<0.001) and DPP-4 inhibitors (13.6% vs. 8.2%; p=0.037) than those with CP, whilst people with CP were more likely to be prescribed insulin (34.9% vs. 19.5%; p<0.001). No differences in prescribing were found for other antihyperglycaemic medication classes.

Conclusion: The differences in prescribing in people with CP compared to AP suggests progressive pancreatic damage and loss of endocrine function, with more patients requiring insulin therapy.
Self-Titration with Insulin Glargine 300 or 100 U/mL has Improved Efficacy vs. Physician-Led Titration—Comparison of the TAKE-CONTROL, ATLANTUS, and ATLAS Studies in People with Type 2 Diabetes (T2DM)

MELANIE JANE DAVIES, EMMANUELLE BOELLE-LS CORREH, MIREILLE BONNEMAIRE, MASATOSHI ODWARA, LUIGI POPESCU, JOCHEM SIEBER, DAVID RUSSELL, SELL-JONES, KRIZSTOF STROJNEK, NIKOLAOS TENTOLOURIS, Leicester, United Kingdom, Chilly-Mazarin, France, Paris, France, Tokyo, Japan, Bucharest, Romania, Frankfurt, Germany, Guildford, United Kingdom, Zabrze, Poland, Athens, Greece, Empowering individuals to self-titrate their basal insulin may help to reduce rates of sub-optimally titrated often observed in clinical practice and help more people achieve HbA1c goals. Here we compare the results from the recently completed TAKE CONTROL study, which evaluated self-titration and physician-led titration of insulin glargine 300 U/mL (Gla-300) in people with T2DM, with comparable studies (ATLANTUS and ATLAS) of insulin glargine 100 U/mL (Gla-100). All 3 studies were 24-week, multicenter, randomized, open-label, parallel-group studies. Fasting blood glucose targets were 80-130 mg/dl (4.4-7.2 mmol/L) in TAKE CONTROL, ≤100 mg/dl (5.5 mmol/L) in ATLANTUS and ≤110 mg/dl (6.1 mmol/L in ATLAS. Mean baseline HbA1c was between 8.4 and 8.9% (Table). Self-titration statistically significantly lowered mean HbA1c by 0.97 ± 1.4% vs. physician-led titration (0.84 ± 1.25%; p < 0.05 for all 3 studies). The incidence of severe hypoglycemia and other safety outcomes was similar between titration arms in all 3 studies (Table). Both Gla-300 and Gla-100 were effective in improving glycemic control. Self-titration with Gla-300 resulted in significantly improved glycemic control vs. physician-led titration, as demonstrated previously with Gla-100, without increased hypoglycemia.

Supported By: Sanofi (EudraCT 2015-001626-42)

Effectiveness of Insulin Glargine U300 Used as Part of Basal Bolus Therapy in People with T2DM—Toujeo 6 Months Real-World Data From Hungary

TIBOR HIDVEGI, PETER STELLA, Győr, Hungary, Paris, France

The Toujeo program demonstrated similar efficacy with lower risk of hypoglycemia (HG) of insulin glargine U300 (Gla-300) compared to insulin glargine U100 in T2DM. Data prospectively collected on real world use of Gla-300 are still of scarce. This single-arm, non-interventional, observational study aimed to describe the effectiveness of Gla-300 in real world setting in people with advanced T2DM. Data on HbA1c, fasting BG, weight (BMI), insulin doses and HG were collected for 6 months in routine clinical care in Hungary from 229 people with T2DM (age: 60.9 years ± 10.4, diabetes duration: 13.4 years ± 7.9, being on insulin for: 7.4 years ± 5.2, HbA1c: 8.9% ± 1.5, BMI: 32.5 kg/m² ± 5.7 [mean±SD]) previously treated with human basal-bolus (BB) regime (NPH+regular insulin) who were switched to analogue BB with Toujeo (U100). Fasting blood glucose targets for self-titration were 80-130 mg/dl (4.4-7.2 mmol/L) in TAKE CONTROL and 90-130 mg/dl (5.0-7.2 mmol/L) in INNOVATE and AUTOMATIX. Fasting blood glucose targets for self-titration were 80-130 mg/dl (4.4-7.2 mmol/L) in TAKE CONTROL and 90-130 mg/dl (5.0-7.2 mmol/L) in both INNOVATE and AUTOMATIX. Self-titration resulted in greater or similar mean HbA1c reductions from baseline vs. physician-led titration (Table). By using self-titration with Gla-300, more people with T2DM achieved fasting glucose targets without confirmed or severe hypoglycemia vs. physician-led titration (TAKE CONTROL and AUTOMATIX). Severe hypoglycemia and other safety outcomes were similar between titration arms in all 3 studies. The effectiveness of Gla-300 and Gla-100 using either a paper or device-based algorithm resulted in improved or similar reductions in HbA1c, without an increased risk of hypoglycemia or safety concerns.

Supported By: Sanofi (EudraCT 2015-001626-42)

Impact of Endogenous Insulin Adjustment Methods on the Assessment of Insulin Pharmacokinetics and Pharmacodynamics

SANG M. CHUNG, JUSTIN A. PENZENSTADLER, MANOJ KHURANA, CHANDRAHAS SAHAJWALLA, Silver Spring, MD

Assessing reliable insulin pharmacokinetics (PK) and pharmacodynamics (PD) following an exogenous insulin administration is a scientific challenge due to the circulating endogenous insulin. Effect of exogenous insulin on the endogenous insulin through the sensitive glucose homeostatic system in the body could further confound the PK/PD data. We compared results of PK/PD parameters of methods in literature for the estimation of insulin PK and PD, namely total method without adjustment (method 1), a simple baseline method (method 2), empirical C-peptide correction method (method 3), conventional PK/PD modeling method (method 5). We also developed new PK/PD modeling method reflecting the effect of glucose on endogenous insulin release based on C-peptide (method 6). Subject-level time-matching insulin and glucose concentrations without external glucose administration were collected from clinical trials with regular human insulin administration to healthy subjects under fasting conditions (n = 23). Primary insulin PK parameters (i.e., the maximum concentration (Cmax) and area under the concentration-time profile (AUC)) were estimated using subjects’ insulin, glucose and C-peptide level data. Our results indicate that insulin AUC and Cmax differ by up to 32%.
and 17%, respectively, among different methods. Further, the contribution of endogenous insulin to total insulin AUC is estimated to be approximately 55% but varies depending upon estimation methods. Insulin PD parameters are apparently similar among different methods (e.g., area under the glucose concentration-time profile, B121.4 and 6293.3 mg/dL-min for method 1-5 and method 6, respectively).

The results call for a careful selection of the method for the assessment of insulin PK and PD parameters depending upon the objectives of study as the relationship between PK and PD could vary among methods and may lead to misinterpretation of data.

1052-P
Real-World Health Outcomes of Insulin Glargine 300 U/mL (Gla-300) vs. Insulin Glargine 100 U/mL (Gla-100) in Patients with Type 1 (T1D) and Type 2 Diabetes (T2D) in the Canadian LMC Diabetes Patient Registry—The REALITY Study
ALEXANDER, ABEIL, RUTH E. BROWN, DSHAY JIANDANI, LUC SAURIOL, RONNIE ARONSON, Toronto, ON, Canada, Laval, QC, Canada
This retrospective cohort study evaluates real-world health outcomes in patients with T1D and T2D initiating Gla-300 or Gla-100 as part of their usual therapy in the largest specialist-led clinic group in Canada, between January 2015 and August 2017. The primary outcome was HbA1c change at 3-6 months. Four separate cohorts were evaluated. In the T1D regimen, 293 patients transferred from Gla-100 to Gla-300 had a significant HbA1c reduction of -0.2 ± 1.2%, with no change in weight, hypoglycemia or basal insulin dose (Table). Similarly, 488 patients with T2D transferred from Gla-100 to Gla-300 had a significant HbA1c reduction of -0.47 ± 1.37%, with no change in weight, hypoglycemia or basal insulin dose. In patients with T2D transferred from NPH or detemir (n=343), Gla-300 had a significantly greater reduction in HbA1c than Gla-100 (0.30 ± 2.2%, with no change in weight, hypoglycemia or basal insulin dose in either group. For insulin-naïve T2D patients (n=1448), there were no significant differences between Gla-300 and Gla-100 in adjusted HbA1c or weight. Patients with T1D and T2D in a national specialist-led registry, who transferred from their usual basal insulin to Gla-300, significantly reduced their HbA1c, without increasing weight, basal insulin dose, nor hypoglycemia incidence.

Table 1

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Baseline</th>
<th>Mean±Δ</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1D: Gla-300 vs. Gla-100 (n=299)</td>
<td>Baseline</td>
<td>8.40±1.56</td>
<td>7.75±1.78</td>
</tr>
<tr>
<td>T1D: Gla-300 vs. Gla-100 (n=488)</td>
<td>Baseline</td>
<td>8.51±1.57</td>
<td>10.73±2.41</td>
</tr>
<tr>
<td>T2D: Gla-300 vs. NPH/detemir (n=343)</td>
<td>Baseline</td>
<td>8.00±1.60</td>
<td>9.60±2.40</td>
</tr>
<tr>
<td>T2D: Gla-300 vs. Gla-100 (n=1448)</td>
<td>Baseline</td>
<td>8.98±1.18</td>
<td>8.56±2.23</td>
</tr>
</tbody>
</table>

1053-P
Electronic Microscopic Findings of Insulin-Induced Local Amyloidosis
SULEYMAN SENDUR, KUBRA CATIPOGULU, OZGE KOKCARA, OZAY GOKDZ, FIGEN KAYMAZ, SELCUK DAGELEN, Ankara, Turkey
Introduction: Insulin-induced local amyloidosis (ILA) was firstly described in 1983, but still underdiagnosed. Here we describe clinicopathological and electron microscopic findings of a case with ILA. Case: A 52-year-old male with type 2 diabetes mellitus for 14 years, on basal-bolus insulin (i.e., insulin lispro and glargine), had noticed 2x2 cm mass at injection site. MRI showed a fibrous mass at the subcutaneous tissue. Punch biopsy of the lesion revealed a fibrous mass at the subcutaneous tissue. Punch biopsy of the lesion revealed both extra- and intracellular amyloid fibrils (Figure 1 A, B).

Discussion: Local amyloid deposition due to insulin injection could be seen in both types of diabetes. Despite earlier reports were associated with porcine insulin, subsequent publications linked also with human insulin and recombinant insulin analogues. High doses of insulin and inappropriate insulin injections are the major risk factors. Extracellular amyloid deposits in ILA arises primarily from exogenous insulin, but the precise mechanism of pathogenicity remains to be established. There are only few case reports of ILA with EM. To the best of our knowledge, here in this case we have firstly showed intracellular accumulation of these amyloid fibrils as well as extracellular compartment, which might have further clinical implications.

Figure 1 A-B.

1054-P
The Impact of Different Initial Insulin Dose Regimens in Short-Term Intensive Insulin Therapy
HUANG XINWEI, Guangzhou, China
Objective: To compare the effects of different initial insulin dose regimens during the short-term intensive treatment in newly diagnosed type 2 diabetes patients, in order to investigate the rational of formula based initiation methods.

Methods: Fifty six patients with newly diagnosed type 2 diabetes, 33 males and 23 females, aged 27-65 years old, BMI 25.43 ± 2.90 kg/m², were randomly assigned into 2 groups: the formula group (whose insulin dose was initiated according to the formula recommended in our previous study, 28 cases) and the empirical group (according to current guidelines, 28 cases). Short-term intensive insulin therapy was performed, and the glycemic goal was gradually achieved. The time to glycemic goal (TGG), TDD-1, the frequency of hypoglycemia and the glycemic variability were compared.

Results: The average TGG in the formula group (2.88 ± 1.44 days) is shorter than that in the empirical group (3.61 ± 1.60 days, P < 0.05). There is no significant difference in the initial insulin dose (44.28 ± 9.10 IU, P = 0.03) of the formula group compared with the TDD-1 (46.91 ± 13.26 IU), whereas the initial insulin dose (34.09 ± 5.21 IU, P < 0.05) of the empirical group is less than TDD-1. Compared with the TDD-1, while 70% of the estimate TDD-1(t-TDD-1), which is calculated according to the formula as the initial insulin regimen, may not meet the requirements (P < 0.001), 100% of the eTDD-1 is also too much for them (P < 0.001). All the indicators for glycemic variability such as mean MBG, MAGE, M value, MAGE and LAGE during the initial three days are not significantly different between the two groups (P > 0.05). There is also no significant difference between 2 groups in the incidence of hypoglycemia (P > 0.05).

Conclusion: Formula based initial insulin regimen is helpful in shortening TGG without increasing within-day glycemic variability or hypoglycemia events. It is recommended that 80% of the eTDD-1 can be used as the initial insulin regimen for the intensive treatment in most newly diagnosed T2DM patients.

Supported By: Sandofi

1055-P
The Challenges and Potential of Digital Therapeutic Solutions for Long-Acting Insulin Management
ARATI KANCHI, LINDA PARKS, TONG SHENG, JANE LEA SMITH, MICHAEL GREENFIELD, Mountain View, CA, Del Mar, CA
Starting on long acting insulin (LAI) can be difficult for people with type 2 diabetes (PW2D). Delayed treatment initiation, imprecision, and poor adherence to therapy can lead to inadequate glycemic control. While emerging digital therapeutic solutions aim to help clinicians and PW2D achieve optimal individualized LAI regimens, real-world use of these solutions remains unknown. In this human factors validation study, we present findings on the Mobile Insulin Dosing System (MIDS), a mobile app module designed to reduce the manual burden of LAI titration. Sixteen PW2Ds (age: 35-70 years) participated in the study. Participants were introduced to MIDS without training. Six real world use scenarios related to LAI management were presented with simulated data. Participants worked through each task using MIDS without assistance. Task performance was measured. Three out of six tasks had 100% success rates and the remaining three tasks had success rates from 73.3-87.5%. Three participants had 100% success rate despite having no prior experience with insulin therapy. All participants endorsed MIDS to be straightforward, easy to use, and effective for insulin management. Among unsuccessful tasks, the individual’s mental model of LAI adjustment was the common root cause. Some PW2Ds did not under-
stand that LAI is adjusted based on the fasting blood glucose (BG) only and assumed that non-fasting BG readings should also be included. Confidence in self-titration was also a risk factor. Overall, MIDS proved to be simple, effective, and easy to use for PWD2Ds of varying ages, LAI experience, and smartphone use. Observed failure risks were related to poor understanding of diabetes and insulin regimens in general and not with the mobile implementation per se. Minimizing these risks, in addition to those inherent to manual recall and entry of BG readings, can enhance the use of digital therapeu- tic solutions for LAI therapy management.

**1056-P**

Real-World Clinical Outcomes of Type 2 Diabetes (T2D) Patients Switching From Insulin Glargine 100 U/mL (Gla-100) or Insulin Detemir (IDet) to Insulin Glargine 300 U/mL (Gla-300) or Insulin Degludec (IDeg)—DELIVER D+ Subgroup Analyses

SEAN D. SULLIVAN, TIMOTHY S. BAILEY, RONAN ROUSSEL, FANG L. ZHOU, ZSOLT BOSNYAK, RON PREBLICK, JUKKA WESTERBACKA, RISHAB GUPTA, LAWRENCE BLONDE, Seattle, WA; Escondido, CA; Paris, France; Bridgewater, NJ; Florham Park, NJ, New Orleans, LA

This retrospective, observational study compared clinical outcomes of adults with T2D switching from Gla-100/IDet to Gla-300 or IDeg. Electronic medical records (Predictive Health Intelligence Environment database) (3/1/15-1/31/17) were analyzed. Switchers with ≥1 A1C during 6-month baseline were propensity score matched on baseline demographic and clinical characteristics (including percentage of patients originally on Gla-100/IDet). Endpoints were A1C change and goal attainment in those with ≥1 A1C test during 3-6-month follow-up, and hypoglycemia (hypo) in all 3184 matched patients. Hypo (ICD-9/10 and/or plasma-glucose level ≤70 mg/dL overall, or associated with an inpatient/ED encounter) was assessed using fixed follow-up (intent-to-treat [ITT], full 6 months) and variable follow-up (on treatment [OT], till discontinuation or 6 months). AIC reduction was comparable between Gla-300 (n=742) and IDeg (n=727) switchers (0.63% and 0.58%, respectively, p=0.49). AIC <7% was attained in 15.1%/16.1% among Gla-300/IDeg switchers, respectively (p=0.63) vs. 44% in 43%/44.4%, respectively (p=0.98). By ITT, switching to Gla-300 (n=1592) reduced hypo incidence (all: 15.6% to 12.7%, p=0.01; inpatient/ED: 5.3% to 3.5%, p=0.01); switching to IDeg (n=1592) resulted in non-significant reductions (all: 14.3% vs. 14.7%, p=0.82; inpatient/ED: 5.3% vs. 4.4%, p=0.56). After adjusting for baseline hypo, no significant differences were found in follow-up between the two groups. By OT, hypo incidence was similar in both groups (adjusted hazard ratio: 1.02 vs. 0.98), but Gla-300 switchers had lower inpatient/ED hypo event rates in follow-up (adjusted rate ratio: 0.56 vs. 0.92).

In a real-world setting of adults with T2D, switching from Gla-100/IDet to Gla-300 or IDeg resulted in comparable improvements in glycemic control and comparable/hyper hyperglycemic outcomes.

Supported By: Sanofi

**1057-P**

Real-World Clinical Outcomes of Type 2 Diabetes (T2D) Patients Switching From Insulin Glargine 100 U/mL (Gla-100) or Insulin Detemir (IDet) to Insulin Glargine 300 U/mL (Gla-300) or Insulin Degludec (IDeg)—DELIVER D+ Subgroup Analyses

SEAN D. SULLIVAN, TIMOTHY S. BAILEY, RONAN ROUSSEL, FANG L. ZHOU, ZSOLT BOSNYAK, RON PREBLICK, JUKKA WESTERBACKA, RISHAB GUPTA, LAWRENCE BLONDE, Seattle, WA; Escondido, CA; Paris, France; Bridgewater, NJ; Florham Park, NJ, New Orleans, LA

DELIVER D+ compared outcomes of patients with T2D switching from Gla-100/IDet to Gla-300 or IDeg. Results from 5 subgroups are reported (overall results in separate abstract).

Electronic medical records (Predictive Health Intelligence Environment database) (3/1/15-1/31/17) were analyzed. Patients had ≥1 A1C during 6-month baseline. Gla-300 and IDeg switchers were propensity score matched on baseline characteristics. Endpoints included A1C change and goal attainment in those with ≥1 A1C test during 3-6-month follow-up, and hypoglycemia (hypo) among all matched patients (6-month fixed follow-up [intent-to-treat]), among the 5 subgroups (Table). The numbers of subgroup patients were similar between the 2 cohorts. There were no significant differences in AIC reduction or goal attainment, or hypo incidence or event rate, between the 2 cohorts, overall or by subgroup. Patients with ≥1AIC≥8% had the best AIC reduction but worst goal attainment. Hypo was greatest among patients at high hypo risk and those with renal impairment.

In a real-world setting of adults with T2D, switching from Gla-100/IDet to Gla-300 or IDeg resulted in comparable improvements in glycemic and hypo-related outcomes in various subgroups, similar to the overall population.

**Table.** AIC and Hypo Outcomes, Overall and by Subgroups.

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Overall</th>
<th>Basal-bolus Patients</th>
<th>Moderate/Severe Renal Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gla-300 vs. IDeg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIC reduction (%)</td>
<td>0.54 vs. 0.58</td>
<td>0.58 vs. 0.51</td>
<td>0.58 vs. 0.61</td>
</tr>
<tr>
<td>AIC ≤7% (%)</td>
<td>(p=0.49)</td>
<td>(p=0.51)</td>
<td>(p=0.61)</td>
</tr>
<tr>
<td>AIC ≤4.8% (%)</td>
<td>(p=0.88)</td>
<td>(p=0.98)</td>
<td>(p=0.98)</td>
</tr>
<tr>
<td>Hypoglycemia incidence (%)</td>
<td>44.3 vs. 44.4</td>
<td>38.2 vs. 43.1</td>
<td>44.0 vs. 52.5</td>
</tr>
<tr>
<td>Hypoglycemia event rate (PPPP)</td>
<td>12.7 vs. 12.7</td>
<td>14.3 vs. 13.1</td>
<td>15.6 vs. 21.1</td>
</tr>
<tr>
<td>Basal-bolus patients</td>
<td>n=736</td>
<td>n=1,805</td>
<td>n=605</td>
</tr>
<tr>
<td>Moderate/Severe Renal Impairment</td>
<td>n=451</td>
<td>n=935</td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia incidence (%)</td>
<td>40.0 vs. 52.5</td>
<td>37.7 vs. 37.7</td>
<td>40.0 vs. 52.5</td>
</tr>
<tr>
<td>Hypoglycemia event rate (PPPP)</td>
<td>12.5 vs. 12.8</td>
<td>12.5 vs. 12.8</td>
<td>12.5 vs. 12.8</td>
</tr>
<tr>
<td>Hypoglycemia incidence (%)</td>
<td>4.1 vs. 3.6</td>
<td>4.4 vs. 5.1</td>
<td>4.1 vs. 3.6</td>
</tr>
<tr>
<td>Hypoglycemia event rate (PPPP)</td>
<td>0.45 vs. 0.47</td>
<td>0.44 vs. 0.47</td>
<td>0.45 vs. 0.47</td>
</tr>
</tbody>
</table>

* "n" was the aggregate of Gla-300 and IDeg switchers. *P* values adjusted for baseline hypo. "eGFR ≤60 mL/min/1.73 m² or nephropathy (ICD-9/ICD-10). *At least one of: "severe hypoglycemic (inpatient/ED) episode within prior 12 months; moderate renal impairment (eGFR 30-59 mL/min/1.73 m²); exposure to insulin for >4 years; recent episode of hypo (ICD diagnosis and/or glucose ≤70 mg/dL within the previous 12 weeks); ED, emergency department; eGFR, estimated glomerular filtration rate, Gla-300, insulin glargine 300 U/mL; AIC, hemoglobin A1c; hypo, hypoglycemia; ICD, International Classification of Diseases; IDeg, insulin degludec; PPPP, person per year.

Supported By: Sanofi

**1058-P**

Mobile-Based Artificial Intelligence Significantly Improves Type 1 Diabetes Management

JOHN DOUPS, VASILIKI PAPANDROPOULOU, SPYRIDOULA GYLKOFRIDI, VASILEDRAS ANGRIANIS, Athens, Greece

Background: Type 1 diabetes involves a multiple decision making process on a daily basis. Mobile technology has been widely spread not only as a mean of communication, but also as multi-usage tool involving a large variety of applications, making everyday life more convenient. "D-Partner" (Diabetes Innovations Ltd) is a mobile based application that serves as a self-management tool for type 1 diabetes, including a bolus wizard (with food database), a basal insulin titration manager, as well as, a large number of automated notifications, warnings or reward messages, according to the data imported by the patient. In addition,"D-Partner" serves as a telemedi- cine tool, as information of meals, insulin dosage, measurements of glucose, blood pressure, body weight, and lab values, may be monitored by the physician through an on-line, web-based platform.

Aim: To investigate the efficacy of "D-Partner" mobile application, in glucose management, in patients with type 1 diabetes.

Methods: 24 patients with type 1 diabetes (14 male, 10 female), with dia- betes duration of 14.2±8.8 years, mean age of 37.4±11.7 years and HbA1c >7%, on basal bolus insulin therapy, were randomized to receive either standard care, or standard care plus the "D-Partner" application usage. HbA1c, somatometric data, blood pressure, heart rate and hypoglycemia frequency data, were obtained at baseline and 3 months after the intervention.

Results: The intervention group presented a significantly improved glu- cose control as recorded by HbA1c reduction, compared to the control group (p=0.01). Additionally, hypoglycemia incidence was significantly lower in the intervention group (p=0.04). There were no significant changes in somato- metric data blood pressure, and heart rate, among the 2 groups.
In a Cox proportional hazards model adjusted for BL and on-trial HbA1c, Lixi BL was lower for Lixi vs. Pbo in pts with micro- or macroalbuminuria (Table).

Lixi vs. Pbo overall or by BL albuminuria status. UACR percent change from baseline (BL) albuminuria status. eGFR was not significantly different for BL and on-trial HbA1c.

The interaction between Tx and baseline (BL) UACR categories was not significant (p<0.01). We assessed change in estimated glomerular filtration rate (eGFR, per the 4-variable modification of diet in renal disease formula) and UACR by BL albuminuria status. eGFR was not significantly different for BL albuminuria status. eGFR was not significantly different for BL albuminuria status.

Conclusions: D-partner, is a mobile based self-management application, that may contribute to a better management of type 1 diabetes, potentially improving the life quality of the patient.

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—NONINSULIN INJECTABLES

Moderated Poster Discussion: Clinical Studies with Noninsulin Injectables (Posters: 1060-P to 1065-P), see page 19.

1060-P
Lixisenatide and Renal Outcomes in Patients with Type 2 Diabetes—A Post-Hoc Analysis of the ELIXA Trial

MARCEL A. MUSKET, LENNART TONNECK, YAO HUANG, MINZHI LIU, ARAMESH SAREMI, HIDDIE LAMBERS, HEERSPINK, DANIEL H. VAN RAALTE, Amsterdam, Netherlands; Somerset, NJ; Pluckemin, NL; Groningen, Netherlands

Limited data exist on long-term effects of GLP-1 receptor agonists on kidney function and albuminuria in T2D. In ELIXA, a study of cardiovascular safety of lixisenatide (Lixi) over a median follow-up of 25 months in 10,426 patients (pts) with T2D and an acute coronary event ≤180 days before screening, slower progression of urinary albumin-to-creatinine ratio (UACR) was associated with lowering incidence of macroalbuminuria beyond glycemic control.

Mean weight loss was 3.4 kg (SD 4.7), and 40.7% (95% CI 0.36-0.46) of patients achieved a composite endpoint of HbA1c/weight reduction of >0.5%/≥2 kg.

Support: By: Sanofi

1061-P
ITCA 650 Provides Consistent Efficacy in T2D Irrespective of Baseline Characteristics—Results of a Pooled Subgroup Analysis

PRAKASH PRABHAKAR, LISE L. KJEMS, HOLLY HUANG, BRIAN SCHWARTZ, MICHELLE A. BARON, Boston, MA; Monistreet, NJ

ITCA 650 consists of a small titanium osmotic mini-pump that is subdermally placed in the abdominal wall during a brief in-office procedure. As an investigational product for the treatment of type 2 diabetes (T2D), ITCA 650 provides a continuous subcutaneous infusion of exenatide over 3 or 6 months. Pooled 39-week data from two double-blind, randomized, Phase 3 studies were used to evaluate the efficacy of ITCA 650 20/60 mcg/d in patients with T2D inadequately controlled by oral antidiabetic drugs (OADs). Results in the overall population (N=663) and in subgroups according to age, gender, BMI, ethnicity, time since diagnosis, baseline HbA1c, GI adverse events, presence of anti-drug antibodies, and renal function are reported. As shown in the Figure, the overall mean (standard deviation [SD]) reduction in HbA1c (%) was 1.5% (1.2) with clinically meaningful reductions in HbA1c consistently observed irrespective of age, gender, BMI, ethnicity, time from T2D diagnosis, and background OADs (data not shown). Patients with a higher baseline HbA1c had a greater response. Mean weight loss was 3.4 kg (SD 4.7) and 40.7% (95% CI 0.36-0.46) of patients achieved a composite endpoint of HbA1c/weight reduction of >0.5%/≥2 kg.

Similar changes were likewise seen consistently across subgroups. ITCA 650 demonstrated consistent efficacy across a wide spectrum of patients with T2D.

Supported By: Intarcia Therapeutics, Inc.
Durability of Combination Therapy with Exenatide and Pioglitazone vs. Basal Bolus Insulin in Poorly Controlled T2DM Patients—Three-Year Follow-Up of the QATAR Study

MUHAMMAD ABDUL-GHANI, OSAMA MIGAHID, SR., AYMAN MEGAHID, SR., MOHAMMAD FAWAZ, MOHAMMAD, RALPH A. DERONZIO, AMIN JAYYOUSI, San Antonio, TX, Dhah, Qatar

Background: We previously demonstrated that addition of exenatide (EXEN) plus pioglitazone (PIO) in poorly controlled T2DM patients on maximal dose of metformin plus sulfonylurea produced a greater A1C reduction at 1 year than basal-bolus insulin. Here we report the 3-year follow-up data.

Methods: 274 poorly controlled T2DM patients (age=56 y; BMI=31; Diabetes duration=11 y, HbA1c=10.1%) on maximal doses of metformin plus SU were randomized to receive: 1) Exenatide once weekly (2 mg) plus pioglitazone (n=142) or 2) basal (glargine)-bolus (aspart) insulin (n=132) to maintain HbA1c below 7%.

Results: In subjects receiving EXEN + PIO, A1c decreased to 6.5% at 6 months, and remained at 6.6% after 36 months. With Insulin Therapy, A1c declined to 7.5% at 6 months and remained 7.3 at 36 months (P<0.001) (Figure). More subjects receiving Insulin Therapy failed to achieve the A1C goal <7% (62% vs. 22%, P<0.0001). Despite lower A1c, subjects receiving EXEN + PIO had lower rate of hypoglycemia (P<0.001) compared to subjects receiving Insulin Therapy. Lastly, subjects receiving Insulin Therapy gained 4.1 kg vs. 1.7 kg (P=0.0002) vs. subjects treated with EXEN + PIO.

Conclusion: Addition of EXEN + PIO in poorly controlled T2DM patients on MET/SU produces greater and more durable HbA1c reduction with lower rate of hypoglycemia compared to Insulin Therapy.

Figure.

Support by: Qatar Foundation (NPRP 5-273-3-079)

Progression from Prediabetes to Type 2 Diabetes (T2DM) in 303 Hypogonadal Men With and Without Testosterone Treatment—Eight-Year-Real-Life Data from a Registry

FARID SAAD, AHNED S. HAIDER, Ankara, Italy, Bremerhaven, Germany

Background: Hypogonadism predicts T2DM and is highly prevalent in men with prediabetes.

Methods: Pooled data from 2 ongoing urological registries. 303 men had prediabetes by HbA1c according to ADA definition. 220 received treatment with 3-monthly injections of testosterone undeconone (TU, T-group), 83 served as controls (CTRL). Anthropometric and metabolic parameters were measured over 8 years.

Results: Mean follow-up: 6.6 years (T-group), 5.6 years (CTRL). Mean age: 60±8.5 years. Under TU, HbA1c decreased from 5.9±0.2 to 5.5±0.3% at 8 years (P<0.001). In CTRL, HbA1c increased from 5.9±0.2 to 6.1±0.06% (P=0.005). At the last observation, all 220 patients (100%) in the T-group had an HbA1c <6.5%. In CTRL, 35 men (42%) had progressed to T2DM with HbA1c >6.5%. The TyG index, a surrogate parameter for insulin resistance, decreased in the T-group from 9.3±0.4 to 9.0±0.4 at 8 years. In CTRL, the index increased from 8.9±0.6 to 9.3±0.4 at 8 years. At baseline, 158 men (52.1%) were obese, 126 men (41.5%) were overweight and 19 (6.3%) had normal weight. Weight decreased from 86.7±12.3 to 89.0±6.8 kg in the T-group and increased from 92.9±10.4 to 98.2±6.3 kg in CTRL. Waist circumference decreased from 104.2±7.1 to 98.2±6.5 cm in the T-group and increased from 102.5±9.7 to 106±3.2 cm in CTRL. Weight loss was 9.2±8.3% at 8 years in the T-group. In CTRL, weight increased by 9.2±3.9% at 8 years (P<0.001 for all). Adherence to TU was 100 per cent as all injections were self-administered.

Conclusion: Testosterone therapy prevented progression from prediabetes to T2DM in hypogonadal men while more than 40% of untreated hypogonadal men developed T2DM. This effect may have been supported by sustained weight loss and been mediated by the invariable increase in lean mass achieved by testosterone.

Supported by: Bayer AG

Identification of Subpopulations Exhibiting the Greatest Cardiovascular Benefit from Long-Acting Glucagon-Like Peptide-1 Receptor Agonists—A Combined Analysis of Large Cardiovascular Outcome Trials

YU MI KANG, YUN KYUNG CHOI, JONG HAN CHOI, CHANG YOUN WOO, WOO JE LEE, JOONG-YEOL PARK, CHANG HEE JUNG, Seoul, Republic of Korea

Background: By combining the results of three large cardiovascular outcome trials (CVDTs) of glucagon-like peptide 1 receptor agonists (GLP-1 RAs), we aimed to investigate the overall effect of GLP-1 RAs on major cardiovascular events (MACE) and identify subpopulations exhibiting the greatest cardiovascular (CV) benefit.

Methods: Three multicenter, randomized, double-blind, placebo-controlled CVDTs of long-acting GLP-1 RAs were included. LEADER (liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes) and EXICAL (Exenatide Study of Cardiovascular Event Lowering). The primary endpoint was three-point MACE (i.e., CV death, non-fatal myocardial infarction, and non-fatal stroke). Overall effect estimates were calculated as hazard ratios (HRs) and 95% confidence intervals (CIs) using the random-effects model; pre-defined subgroup analyses were performed.

Results: Overall, significant risk reductions in MACE (relative risk [RR]: 0.85 [95% CI: 0.81-0.87]) and CV death (RR: 0.89 [95% CI: 0.75-0.95]) were observed. Subgroup analysis indicated significant racial differences in this CV benefit (P for test of difference < 0.001). Risk reductions were observed in subjects of black race (RR: 0.78 [95% CI: 0.60-0.99]) and Asians (RR: 0.35 [95% CI: 0.09-1.30]). However, post-hoc analysis using Bonferroni correction revealed that only Asians exhibited a significantly greater CV benefit from treatment, compared with subjects of white race (P<0.001).

Conclusions: Long-acting GLP-1 RAs reduced risks of MACE and CV deaths in diabetic study populations, and racial difference in the CV benefit was observed. The existence of extra CV benefit in Asians and the underlying mechanisms should be investigated in the future.

Supported by: Qatar Foundation (NPRP 5-273-3-079)

Rates of Major Adverse Cardiovascular (CV) Events (MACE) and Mortality with Basal Insulin by Liraglutide Use—A DEVOTE Sub-analysis

KIRSTINE BROWN-FRANDSEN, SCOTT S. EMERSON, STEVEN P. MARSRO, DARREN K. MCGUIRE, THOMAS R. PIEBER, NEIL R. POULTER, BERNARD ZINMAN, Republic of Korea

In the LEADER trial, the GLP-1 analog liraglutide significantly reduced risks of MACE and mortality vs. placebo in patients with type 2 diabetes (T2D) and high CV risk. This post-hoc analysis compared effects of concomitant liraglutide vs. no liraglutide use on MACE and mortality in 7637 patients with T2D and high CV risk randomized 1:1 to degludec/glargine U100 in DEVOTE (NCT01959529). Hazard ratios (HRs) for MACE/mortality were calculated using a Cox regression model adjusted for treatment and time-varying liraglutide use at any time in the trial, without interaction. Sensitivity analyses adjusted for baseline covariates including age, sex, smoking, T2D duration, CV risk, insulin therapy, AIC, LDL, HDL and liver/kidney function. At baseline, 436 (5.7%) patients were on liraglutide: 187 (2.4%) started and 210 (2.7%) stopped liraglutide thereafter. Mean liraglutide exposure from randomization to follow-up was 731 days. Liraglutide use was associated with significantly lower HRs for MACE and mortality vs. no liraglutide use (Table). HRs from sensitivity analyses were consistent with these results. Thus, liraglutide was asso-
Clinically significant lower MACE and mortality rates in basal insulin users.

Table: MACE and all-cause mortality by lagirudine use in DEVOTE

<table>
<thead>
<tr>
<th></th>
<th>Deleglude/glargine U100 with concomitant lagirudine use</th>
<th>Deleglude/glargine U100 without concomitant lagirudine use</th>
<th>Lagirudine use vs no lagirudine use (HR [95% CI])</th>
<th>Two-sided p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MACE</strong></td>
<td>25</td>
<td>2.91</td>
<td>0.62 [0.41-0.92]</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>656</td>
<td>4.74</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Events per 100 patient years of observation</strong></td>
<td><strong>Events per 100 patient years of observation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CV death</strong></td>
<td>8</td>
<td>0.91</td>
<td>0.67 [0.23-1.96]</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>270</td>
<td>1.90</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Non-fatal MI</strong></td>
<td>15</td>
<td>1.73</td>
<td>0.82 [0.59-1.19]</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td>298</td>
<td>2.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
<td>13</td>
<td>1.48</td>
<td>0.95 [0.50-1.79]</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>410</td>
<td>2.88</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HFrEs presented are for the time to the first confirmed event (in days).

**1067-P**

**Robust Glucose Control and Weight Loss after Six Weeks of Treatment with MEDI0382, a Balanced GLP-1/Glucagon Receptor Dual Agonist, in Patients with Type 2 Diabetes**

**PHILIP AMBERY, MICHAEL W. STUMVOLL, MAXIMILIAN G. POSCH, TIM HEISE, LEO NIA FRIEDMANN, LAN FENG TSOAI, DARREN ROBERTSON, MARCELLA PETRONE, CRISTINA RONDINONE, VICTORIA E. PARKER, BAZI HIRSBERG, LUTZ JERMUTUS, Cambridge, United Kingdom, Leipzig, Germany, Berlin, Germany, Neuss, Germany, Mainz, Germany, Gaithersburg, MD**

MEDI0382 is under development for the treatment of type 2 diabetes mellitus (T2DM). In a double-blind study (NCT02548595), 51 T2DM patients with BMI 27-40 kg/m² were randomized (1:1) to daily SC MEDI0382 200 µg or placebo (PBO). Based on ANCOVA with treatment and baseline (BL) values as covariates, MEDI0382 markedly reduced fasting glucose (change from BL at day 41, -49.9 vs. -19.2 mg/dL, F = 0.0001) and postprandial glucose in a mixed-meal tolerance test (percent change from BL in glucose AUC, -32.8 vs. -10.2; P < 0.0001) (Figure 1) with no increase in hypoglycemia. HBAlc levels decreased -0.9% with MEDI0382 and -0.6% with PBO (P = 0.0004). Weight loss was 3.8 kg vs. BL (1.7 kg vs. PBO; P = 0.0008) 92% of MEDI0382 patients lost >2 kg. Mean reduction in ambulatory systolic BP was -4.2 for MEDI0382 vs. -1.5 mmHg for PBO (P = ns). As with marketed GLP-1 agonists, a mean pulse increase of 8.8 BPM for MEDI0382 vs. a fall of 2.0 BPM for PBO was seen (P < 0.0001). Treatment-related AEs such as decreased appetite, vomiting, and headache were seen in more patients on MEDI0382 (20 vs. 15); 0 were grade >3 severity. 3 led to study discontinuation for MEDI0382 vs. 1 for PBO, and 1 SAE in the PBO arm. Overall, MEDI0382 normalized fasting and postprandial blood glucose, significantly reduced body weight, and had an acceptable safety profile over 41 days of dosing in obese/overweight T2DM patients.

**1066-P**

**Lesser eGFR Decline with Dulaglutide Regardless of Weight Changes in People with Type 2 Diabetes and Moderate to Severe Chronic Kidney Disease (AWARD-7)**

**KATHERINE R. TUTTLE, MARK LAKSHMANAN, BRIAN L. RAYNER, ROBERT S. BUSCH, ALAN G. ZIMMERMANN, BRAD WOODWARD, FADY T. BOTROS, SPOKANE, WA, Indianapolis, IN Cape Town South Africa Albany, NY**

Body weight (BW) changes may affect muscle mass and thus creatinine (Cr) levels. Estimating glomerular filtration rate (eGFR) by Cr-based equations may not accurately reflect changes in kidney function when BW changes. Dulaglutide (DU) treatment was associated with BW loss and lesser eGFR (Cr-COCK-EPID) decline in people with T2D and moderate to severe CKD compared to insulin glargine (IG) (Table). The aim was to evaluate if the lesser eGFR decline observed with DU is related to BW loss. eGFR was evaluated with Cr-based equations (MDRD, CKD-EPI) compared to cystatin C (C-CKD-EPI) equation. Cystatin C is not affected by muscle mass changes. CrCL was evaluated with the Cockcroft-Gault equation. BL characteristics were similar between treatments (mean±SD) eGFR (Cr-CKD-EPI): 38.3±12.8 mL/min/1.73m², A1c: 8.6±1.0%, age: 64.6±8.6 y, T2D duration: 18.1±8.7 y).

All equations consistently show that eGFR remained stable with DU, but significantly decreased with IG regardless of BW loss in DU or gain in IG (Table). Since BW is a factor in CrCL calculations, compared to eGFR equations, BW loss in DU led to bias toward greater reductions in CrCL. This bias disappeared when using lean BW (Table).

In conclusion, compared to IG, DU was associated with lesser eGFR decline in people with T2D and moderate to severe CKD regardless of BW changes.

**Relative Contribution of Basal and Postprandial Hyperglycemia Stratified by A1c Categories Before and After Treatment Intensification with Dulaglutide**

**GUILLERMO E. UMPIERREZ, KEVIN M. PANTALONE, CHARLES ATISSO, LAURA FERNANDEZ LUNDO, HIREN PATEL, Atlanta, GA, Cleveland, OH, Indianapolis, IN Dulaglutide (DU) has demonstrated non-inferiority vs. lagirudine (LIR) and superiority vs. exenatide BID (EIX) in A1c reduction. No data are available on how GLP-1RAs affect the relative contribution of basal hyperglycemia (BHG) and post-prandial hyperglycemia (PPHG) to overall hyperglycemia (OHG) across A1c categories. Data from five phase 3 studies (N=673) were stratified by A1c categories before and after DU treatment intensification with MEDI0382, a Balanced GLP-1/Glucagon Receptor Dual Agonist, in Patients with Type 2 Diabetes**

**Robust Glucose Control and Weight Loss after Six Weeks of Treatment with MEDI0382, a Balanced GLP-1/Glucagon Receptor Dual Agonist, in Patients with Type 2 Diabetes**
1069-P

Achieving Composite Endpoint of A1C <7.0% without Weight Gain or Hypoglycemia with Once-Weekly Dulaglutide in Chinese Patients with Type 2 Diabetes—Post-Hoc Analysis

XINHUA XIAO, CHANGJIANG WANG, FENG WANG, PENGFEI LI, LIQUN GU, Beijing, China; Hefei, China; Shanghai, China

This post-hoc analysis of 2 randomized trials of the once weekly glucagon-like peptide-1 receptor agonist dulaglutide (DU) assessed the proportion of Chinese patients with type 2 diabetes (T2D) achieving a composite endpoint of glycated hemoglobin (A1C) <7.0%, no weight gain (<0 kg), and no hypoglycemia (confirmed glucose ≤3.9 mmol/L or report of severe hypoglycemia) after 26 or 52 weeks of treatment with DU 1.5 mg or 0.75 mg vs. glimepiride (GLIM) or insulin glargine (GLAR). Patients in the DU vs. GLIM study (n = 556) were treatment-naïve or discontinued from oral monotherapy; those in the DU vs. GLAR study (n = 591) continued on metformin and/or sulfonylurea. Analyses in each trial were on modified intent-to-treat population; missing values were imputed using last observation carried forward. Significantly (p<.001, Fisher’s exact test) more patients achieved the composite endpoint with DU 1.5 mg or 0.75 mg vs. GLAR after 26 weeks (47.8% and 39.5% vs. 14.9%) and after 52 weeks (26.0% and 23.0% vs. 8.7%). Similar results were observed for composite endpoints of A1C <7.0% and no weight gain, and A1C <7.0% and no hypoglycemia. Dulaglutide is an effective treatment option for Chinese patients with T2D, resulting in a large proportion of patients reaching A1C targets without weight gain or hypoglycemia.

Figure.
Comparative Glycemic Effectiveness of Dulaglutide vs. Liraglutide and Exenatide QW in a U.S. Real-World Setting

Reema Modi, Qing Huang, Maria Yu, Hiren Patel, Ruizhi Zhao, Michael Grabner, Laura Fernández Landoo, Indianapolis, IN; Wilmington, DE; Toronto, ON; Canada.

The objective of this retrospective observational study was to compare 6-month and 1-year real-world glycemic effectiveness among patients initiating GLP-1 receptor agonists (GLP-1RA), dulaglutide (DULA) vs. liraglutide (LIRA) or DULA vs. exenatide QW (EQW), using U.S. claims data from the HealthCore Integrated Research Database (HCIRD)® between November 2014 and May 2016 (date earliest GLP-1RA fills date).

Patients ≥18 years old, with T2DM, no claim for any GLP-1RA in the 6 months pre-index period (baseline), continuous enrollment 6 months pre- and 1-year post-index, ≥1 HbA1c result pre-index and 1-year post-index were included. DULA users were propensity-matched 1:1 to LIRA (595 pairs) or EQW (422 pairs) users. Matched cohorts were balanced in baseline patient characteristics including mean HbA1c. The mean age of all cohorts was 53 years and approximately 50% were males. Among the DULA vs. LIRA matched cohorts, 59% and 41% initiated on DULA 0.75mg and 1.5mg QW, respectively. The key effectiveness results are included in the Table.

At both 6-month and 1-year post-index, patients initiating DULA experienced a greater reduction in HbA1c compared to LIRA or EQW initiators (p <0.05). In all cohorts, patients adherent to their GLP-1RA treatment had greater reductions in HbA1c than non-adherent patients (p <0.05).

Table. Real-World Glycemic Effectiveness Outcomes among GLP-1RA Initiators.

<table>
<thead>
<tr>
<th>Matched DULA vs. LIRA cohorts</th>
<th>Matched DULA vs. EQW cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td>DULA</td>
<td>LIRA</td>
</tr>
<tr>
<td>6-month post-index outcomes¹</td>
<td>420</td>
</tr>
<tr>
<td>HbA1c Outcomes, mean (SD)</td>
<td>8.71 (1.76)</td>
</tr>
<tr>
<td>Change in HbA1c from baseline</td>
<td>-1.10 (1.07)</td>
</tr>
<tr>
<td>Change in HbA1c among adherent patients³</td>
<td>-1.25 (1.07)</td>
</tr>
<tr>
<td>Change in HbA1c among non-adherent patients³</td>
<td>-0.75 (1.79)</td>
</tr>
<tr>
<td>12-month post-index outcomes²</td>
<td>595</td>
</tr>
<tr>
<td>HbA1c Outcomes, mean (SD)</td>
<td>8.78 (1.02)</td>
</tr>
<tr>
<td>Change in HbA1c from baseline</td>
<td>-1.07 (1.07)</td>
</tr>
<tr>
<td>Change in HbA1c among adherent patients³</td>
<td>-1.25 (1.08)</td>
</tr>
<tr>
<td>Change in HbA1c among non-adherent patients³</td>
<td>-0.68 (1.79)</td>
</tr>
</tbody>
</table>

* Significant difference in mean HbA1c change between the matched cohorts with p value <0.05. † Significant difference in mean HbA1c change between adherent and non-adherent patients within each cohort with p value <0.05

The study included only exenatide QW pen users. Assessed among subgroup of patients with 6-month post-index HbA1c results (between index date + 93 days and index date + 228 days). Pre-index HbA1c results were obtained between index date - 183 days and index date + 14 days. Adherent patients were defined as those with proportion of days covered (PDC) ≥80% at 6-month post-index. Assessed among patients with 1-year post-index HbA1c results (between index date + 275 days and index date + 410 days). Adherent patients were defined as those with proportion of days covered (PDC) ≥80% at 1-year post-index.

Supported By: Eli Lilly and Company

Near-Normoglycemia, with Meaningful Discontinuations of Prandial Insulin, by Adding Weekly Albiglutide (Albi) to Uncontrolled Basal/Bolus Insulin-Treated Type 2 Diabetes (T2DM)

Julio Rosenstock, Antonio J. Nino, Joseph Soffer, Jason M. Mallory, Luis M. Erskine, Andrea Acusta, Jodi Dole, Molly Carr, Philip Home, Dallas, TX; Chester Springs, PA; Collegeville, PA; King of Prussia, PA; Newcastle upon Tyne, United Kingdom.

The glycemic efficacy of weekly Albi 50 mg to replace prandial insulin lispro (Lis) was evaluated in T2DM inadequately controlled on a multiple daily insulin regimen (≥3 injections/day). Basal/bolus insulin was evaluated during a 4 week run-in phase before randomization to: 1) Albi + optimized insulin glargine (Gla), with prandial Lis subsequently discontinued by week 4 (n = 402) or 2.) optimized Lis + optimized Gla (n = 412). At 26 week, the LS mean ± SE change from baseline in HbA1c was −1.04 ± 0.04 vs. −1.10 ± 0.04 (treatment difference 0.06 [95% CI, −0.05, 0.17%], non-inferiority p <0.0001) (Table). In the Albi + Gla group, 218 subjects (54%) replaced all prandial insulin without reintroducing Lis through to 26 week, resulting in a total daily insulin dose reduction of 61 U. Mean number of injections was reduced from 29 to 13 (mean change ± SE: −18 ± 8) per week. GI adverse events were higher in the Albi group (26% vs. 13%). Albi + Gla was favorable for both severe or moderate systemic hypoglycemia (230 [57%] vs. 309 [75%]) and weight change (LS mean ± SE: −2.0 ± 0.2 vs. +2.4 ± 0.2 kg; p <0.0001) vs. Lis + Gla.

In conclusion, Albi meaningfully improved glucose control; prandial insulin was stopped in 54% of participants, allowing substantial reductions in insulin dose and number of injections, less hypoglycemia, and body weight loss.

Supported By: Sanofi U.S.

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—NONINSULIN INJECTABLES

1072-P Relationship of Ethnicity to Clinical Outcomes in iGlarLixi-Treated Patients with Type 2 Diabetes

Pablo Ayora, Jason Chad, Aramesh Saremni, Terry A. Dex, Michelle Roberts, Guillermo E. Umphierrez, Dallas, TX; Bridgewater, NJ; Atlanta, GA.

Pharmacogenetic studies have shown significant differences among racial and ethnic groups. This post-hoc analysis of 2 30-week phase 3 trials of patients with type 2 diabetes uncontrolled on metformin ± oral antidiabetic drugs (OADs) (iLixiLan-O: NCT02058147) or basal insulin ± OADs (iLixiLan-L: NCT02058160) determined the safety of iGlarLixi vs. insulin glargine (iGlar) among Hispanic and non-Hispanic patients.

Analysis of variance/co-variance was used for continuous variables and χ²/Cochran-Mantel-Haenszel for categorical variables. A generalized linear model using negative binomial distributions with factors of treatment arm and ethnicity, covariates of age and baseline weight or BMI, and log exposure as offset, was used for symptomatic hypoglycemia (plasma glucose ≤70mg/dL) rates. Adjusted hypoglycemia rates used the same model with mean values of age and baseline weight or BMI.

Across studies 20% (353/1730) of all patients were Hispanic. At baseline, Hispanic patients had significantly lower body weight, BMI, and fasting plasma glucose vs. non-Hispanic patients (all, P<0.001). Overall, clinical outcomes were similar for Hispanic and Non-Hispanic patients, regardless of drug type (Figure). However, iGlarLixi demonstrates better glycemic control in both Hispanic and non-Hispanic patients, with similar safety outcomes to iGlar.

Supported By: Sanofi U.S.
Effect of Single Dose of Insulin Glargine/Lixisenatide Fixed-Ratio Combination (iGlarLixi) on Postprandial Glucodynamic Response in Japanese Patients with Type 2 Diabetes Mellitus

MÉGUMI INOUE, MARTÍN LORENZ, HIDEYA MUTO, YASUHIRO HASHIMOTO, Fukuda, Japan, Frankfurt, Germany, Tokyo, Japan

Fixed ratio combination of insulin glargine/lixisenatide (iGlarLixi) is expected to bring benefits such as better efficacy, mitigating barriers to their individual use, and convenient single daily injection. Based on the study results which demonstrated the efficacy and safety of iGlarLixi, approvals from FDA and EMA were obtained. Currently, specific clinical development of iGlarLixi in Japan is ongoing. A randomized, open-label, placebo-controlled, 4-sequence, 4-period, 4-treatment crossover study to investigate the postprandial glucodynamic response to single subcutaneously (SC) dose of iGlarLixi in Japanese T2DM patients was conducted. This study primary aimed at investigating the PD of lixisenatide at doses up to 10 µg with insulin glargine as compared to placebo and low-dose insulin glargine alone in Japanese T2DM patients. Twenty patients were assigned to one of the four sequences of treatments, all of which included iGlarLixi (5 U/5 µg and 10 U/10 µg), 5 U insulin glargine and placebo. The parameter FPG-AUC,2h was evaluated as primary endpoint. The LS mean differences of FPG-AUC,2h between iGlarLixi (5 U/5 µg) and placebo, iGlarLixi (10 U/10 µg) and placebo, iGlarLixi (10 U/10 µg) and iGlarLixi (5 U/5 µg) and 5 U insulin glargine were -7.48 (p < 0.0001), -10.75 (p < 0.0001), -3.28 (p < 0.0001), and -7.30 (p < 0.0001), respectively. These results demonstrated the 2 doses of iGlarLixi significantly decreased PPG in a dose-dependent manner following a standardized breakfast when compared to placebo. And by combining the complementary therapeutic benefits of insulin glargine predominantly on FPG and the effect of lixisenatide on PPG, the combination product can affect both components of hyperglycemia as a therapeutic principle. No SAEs were reported and no patients discontinued the study. Single SC doses of iGlarLixi were safe and well tolerated. Supported By: Sanofi K.K.
1077-P
Medication Compliance on Glycemic Control in Patients with Elevated HbA1c
AHMED ELHASSAN, MARCONI ABREU, ANNA TUMYAN, OLIVIA PAPACOSTEA, KATHERINE PEICHER, PHINHAN DAOCHHIKE, MUHAMMAD S. SIDDIQUI, BEVERLY ADAMS-HUET, XILONG LI, LAURENTIU POP, IDIKCO LINGYAVIYI, Dallas, TX; ROTUNDIA, CA; OKLAHOMA CITY, OK; MCKINNEY, TX

The simple study was a randomized trial comparing two treatment strategies (basal insulin (BI) + GLP-1 RA vs. basal-bolus insulin (BBI) in patients with T2DM and very elevated HbA1C (>10%). The glucose lowering agents were provided free of charge for the 6-month study. This post-hoc analysis evaluates compliance with the assigned glucose lowering agents, and the effect of compliance on glycemic control. Compliance was assessed by inventory of the returned medication. Optimal compliance was defined as >80% use of the respective agent over the entire duration of the study. Mixed model repeated measures analysis with compliance as a covariate was used to evaluate the treatment effect on HbA1C.

The 120 randomized patients had a mean (SD) age 47.4 (9.5) years, BMI 37.2 (10.3) kg/m², and baseline HbA1C 12.1 (1.4)%. The proportion of patients with optimal compliance with basal insulin was numerically higher in the BI+GLP-1 RA group (p=0.16); optimal compliance with GLP-1 RA was higher compared to basal insulin (p=0.04) (Table). Compliance was an independent predictor for glycemic improvement (P = 0.008); treatment with BI+GLP-1 RA was superior to lowering HbA1C after adjustment for compliance (P = 0.01).

Optimal compliance was low in this patient population. While compliance was a significant contributor to glycemic control, treatment with BI+GLP-1 RA improved HbA1C more than BBI independent of medication compliance.

Table. Patients With Optimal Compliance With Glucose Lowering Agents (>80% Over the 6-Month Study Duration) in the Two Treatment Groups (Basal Insulin + GLP-1RA Compared With Basal-Bolus Insulin) and the Effect of Compliance on Glycemic Control.

<table>
<thead>
<tr>
<th>Compliance Subgroup</th>
<th>Basal-Bolus Group (n=55)</th>
<th>Basal Insulin + GLP-1RA Group (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal Insulin</td>
<td>8 (14.3)</td>
<td>14 (25.9)</td>
</tr>
<tr>
<td>Basal Insulin</td>
<td>6 (10.7)</td>
<td>NA</td>
</tr>
<tr>
<td>GLP-1RA</td>
<td>NA</td>
<td>14 (25.9)</td>
</tr>
<tr>
<td>Change in HbA1c:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted for compliance</td>
<td>-3.1 (-4.0,-2.2)</td>
<td>-4.5 (-5.2, -3.8)</td>
</tr>
<tr>
<td>Optimal Compliance subgroup</td>
<td>-3.1 (-4.8,-1.6)</td>
<td>-5.4 (-6.6, -4.2)</td>
</tr>
<tr>
<td>Low Compliance subgroup</td>
<td>-3.0 (-3.7,-2.3)</td>
<td>-3.6 (-4.4,-2.8)</td>
</tr>
</tbody>
</table>

Data are least squares means (95% CI) or n (%); NA - Not applicable. Compliance data available for n=110 (intention-to-treat analysis sample).

1078-P
Safety and Efficacy of Exenatide Therapy for the Management of Hospitalized Patients with Type 2 Diabetes—Exenatide Hospital Trial
MAYA PAYYMAAN, DARA L. MIZE, DANIEL J. RUBIN, ISABEL ANZOLA, MARIA A. URIUTIA, CLEMENTINA RAMOS, FRANCISCO J. PASQUEL, J. SONYA HAW, PRIVATHAMA VELANKI, HEGIUNG WANG, KATHERINE E. JOYCE, ABHIJANA KARUNAKARAN, BONNIE S. ALBURY, RITA WEAVER, LAVALYA VISWANATHAN, SHUCHIE JAGGI, RODOLFO J. GALINDO, GUILLERMO E. UMPIERREZ, Atlanta, GA; Nashville, TN; Philadelphia PA; Decatur, GA; Pittsburgh PA

This pilot multi-center, open-label, randomized trial determined the safety and efficacy of exenatide alone or in combination with basal insulin in medicine and surgery patients with type 2 diabetes (T2D). A total of 150 patients with blood glucose (BG) between 140-400 mg/dl on home therapy with oral agents or insulin ≤ 0.5 U/kg/day were treated with exenatide, exenatide+basal, or basal-bolus (BB) regimen. Exenatide was started at 5 mcg BID, basal insulin at 0.25 U/kg/d, and BB at 0.5 U/kg/d given half as glargine and half as lispro before meals. At discharge, pre-admission therapy was restarted and patients were randomized to exenatide (titrated to 10 mcg BID) or basal insulin, and followed for up to 3 months.

The combination of exenatide and basal insulin resulted in lower hospital mean daily BG and higher proportion of target BG 70-180 mg/dl compared to exenatide or BB, p<0.01 (Table). There were no differences in hospital hypoglycemia, gastrointestinal (GI) adverse events or study withdrawal between groups. After discharge, there was no difference in BG control (p=0.65) but exenatide group had more GI adverse events (p=0.001) compared to basal group.

These preliminary results indicate that inpatient and post-discharge treatment with exenatide in combination with basal insulin is safe and effective for the management of general medicine and surgery patients with T2D.

1079-P
Effect of Dulaglutide and Long-Acting Insulin Combination Therapy in Patients with Type 2 Diabetes
YOSHINOBU KONDO, SHINOBU SATOH, YASUO TERAUCHI, ChiTAGAKI, Japan, YOKOHAMA, Japan

Objective: In patients with diabetes, the use of GLP-1 receptor agonist expected to decreases the number of injections and improves blood glucose control. In this study, the effects were evaluated when changed from intensive insulin therapy to combination therapy of long-acting GLP-1 receptor agonist, dulaglutide, and long-acting insulin.

Methods: We examined patients with type 2 diabetes who were admitted to our department and started blood glucose management with intensive insulin therapy, followed by flash glucose monitoring (FGM); we then switched to dulaglutide + long-acting insulin therapy. We analyzed the blood glucose excursion on intensive insulin therapy, 5 and 12 days after dulaglutide + long-acting insulin combination therapy change. Furthermore, we evaluated HbA1C and GA after 1 month of the change.

Result: We enrolled 20 patients with type 2 diabetes (age: 70.1 ± 11.1 years; history of diabetes: 20.8 ± 9.27 years). The blood glucose excursions during intensive insulin therapy and 5 and 12 days after dulaglutide + long-acting insulin combination therapy were 134.3 ± 43.1, 125.4 ± 28.2, and 110.1 ± 22.5 mg/dl, respectively. A significant decrease was observed in the blood glucose average on the day of intensive insulin therapy and 5 days after dulaglutide + long-acting insulin combination therapy. In addition, the blood glucose average was significantly decreased between days 5 and 12 after the dulaglutide + long-acting insulin combination therapy. Furthermore, we analyzed the blood glucose standard deviation exhibited a declining trend after changing to dulaglutide + long-acting insulin combination therapy. After 1 month of the change, HbA1c and GA decreased significantly (-1.37% ± 1.87%, P = 0.007 and -7.01% ± 4.51%, P = 0.016, respectively).

Conclusions: The transition from intensive insulin therapy to dulaglutide + long-acting insulin therapy demonstrated better blood glucose control with reduced blood glucose excursion and the number of self-injections.

1080-P
Effects of Dulaglutide and Trelagliptin on Beta-Cell Function in Patients with Type 2 Diabetes—The DUET-Beta Study
YOSHINOBU KONDO, SHINOBU SATOH, YASUO TERAUCHI, Yokohama, Japan, Chigaasaki, Japan

Some studies of glucagon-like peptide 1 receptor agonists (GLP-1-RA) and dipeptidyl peptidase-4 inhibitors (DPP-4-I) have shown positive effects...
on beta-cells. A direct comparison between weekly GLP-1-RA: dulaglutide (Dula) and weekly DPP-4-i: trelagliptin (Trela) effects on beta-cell function has not yet been performed. We compared the effects of Dula and Trela on beta-cell function in type 2 diabetes (T2D) patients in an open-label, parallel-group, randomized controlled trial. Patients received Dula 0.75 mg/week or Trela 100 mg/week for 24 weeks. Beta-cell function was assessed using a glucagon stimulation test (GST)-based disposition index (DI = area under the curve of C-peptide during 6 min GST + HOMA2-IR). The primary endpoint was the difference between the two groups in the change in DI over the 24-week treatment period. Body composition was assessed using the bioelectrical impedance method. Fifty metformin ± basal insulin-treated patients with T2D were randomized to Dula or Trela. Forty-eight patients completed 24 weeks of weekly administration of Dula (n = 23) or Trela (n = 25). The change in DI during 24 weeks was not different between the groups (Dula: -0.34 ± 0.49, Trela: -0.57 ± 0.47, p = 0.74). However, the change in HOMA2-%B was higher in the Dula group than in the Trela group (Dula: +50.8 ± 9.9% vs. Trela: +75 ± 9.5%, p = 0.033). HbA1c decreased to a greater extent in the Dula group (Dula: -0.77 ± 0.07%, Trela: -0.57 ± 0.07%, p = 0.04). Body weight reduced more in the Dula group than the Trela group (Dula: -1.4 ± 0.3 kg vs. Trela: -0.3 ± 0.3 kg, p = 0.02). Body fat mass reduced more in the Dula group than the Trela group (Dula: -1.2 ± 0.3 kg vs. Trela: -0.3 ± 0.2 kg, p = 0.02). Dula did not reduce skeletal muscle mass (-0.2 ± 0.1 kg, p = 0.31).

In conclusion, the effects of Dula and Trela on beta-cell function were not different in GST-based DI. However, Dula increased the HOMA2-%B level more than Trela. Dula reduced body fat mass without causing skeletal muscle mass loss.

1081-P Consistent HbA1c and Body Weight Reduction with Semaglutide Independent of Diabetes Duration—SUSTAIN 1-5 and 7 Patient-Level Meta-analysis

JULIO ROSENSTOCK, LOUIS B. CHAYKIN, JOERG LUEDEMANN, STEN MADSBAD, SR, JULIE F. LARSEN, EMRE YILDIRIM, STEPHEN C. BAIN, Dallas, TX; Bra-denton, FL; Falkensee, Germany; Copenhagen, Denmark; Sabborg, Denmark; Swansea, United Kingdom

Achieving glycomic targets is challenging, and responsiveness to therapy may diminish over time in T2D. Semaglutide, a new once-weekly GLP-1 analog for T2D treatment, showed superior reductions in HbA1c and body weight (BW) in SUSTAIN 1-5 and 7 clinical trials vs. placebo or active comparators. This meta-analysis assessed the efficacy and safety of semaglutide 0.5 mg (BW) in SUSTAIN 1-5 and 7 clinical trials vs. placebo or active comparators. The change in HbA1c from baseline at 26 weeks of weekly administration of Dulaglutide (n = 23) or Trelagliptin (n = 25). The change in BW from baseline was +7.5 ± 9.5%, p = 0.003. HbA1c decreased to a greater extent in the Dula group (Dula: -0.77 ± 0.07%, Trela: -0.57 ± 0.07%, p = 0.04). Body weight reduced more in the Dula group than the Trela group (Dula: -1.4 ± 0.3 kg vs. Trela: -0.3 ± 0.3 kg, p = 0.02). Body fat mass reduced more in the Dula group than the Trela group (Dula: -1.2 ± 0.3 kg vs. Trela: -0.3 ± 0.2 kg, p = 0.02). Dula did not reduce skeletal muscle mass (-0.2 ± 0.1 kg, p = 0.31).

In conclusion, the effects of Dula and Trela on beta-cell function were not different in GST-based DI. However, Dula increased the HOMA2-%B level more than Trela. Dula reduced body fat mass without causing skeletal muscle mass loss.

1082-P LIRA-PRIME Trial Design and Baseline Data—Efficacy in Controlling Glycemia with Liraglutide in a Primary Care Setting

JEFF UNGER, DEREK LOWE, GERRI MURPHY, JAYANT KUMAR PANDA, MEHMET SARGIN, MARGIT KALTFOFT, MARIANNE TREPENDAHIL, MAROUDIAN ZOGHBI, Rancho Cucamonga, CA; Surrey, BC, Canada; Mount Pearl, NL, Canada; Cuttack, India; Istanbul, Turkey; Sabborg, Denmark; Beirut, Lebanon

Despite the majority of patients with type 2 diabetes (T2D) being treated in primary care, clinical evidence to guide treatment decisions is still scarce in this setting.

LIRA-PRIME (NCT027230377), a 104-week, randomized (1:1), open-label, active-controlled trial in primary care, compares the efficacy of liraglutide vs. oral antidiabetic drugs (chosen by the investigator) in controlling glycemia in patients with T2D inadequately controlled with metformin alone. Besides an A1C of 7.5-9.0% within 90 days prior to screening, the pragmatic approach of the trial includes few inclusion and exclusion criteria, treatment according to local labels, quarterly visits after week 25, and trial product dispensing by retail pharmacy. Primary endpoint is time to inadequate glycemic control, defined as A1C >7.0% at two scheduled consecutive visits after the first 26 weeks of treatment.

The trial randomized 1997 patients from 9 countries. The broad distribution of baseline characteristics, e.g., age range of 19.0-89.0 years, reflects the study design and heterogeneity of patients treated in primary care (Table). LIRA-PRIME will provide data currently lacking from primary care regarding the efficacy of liraglutide in controlling glycemia in patients with T2D inadequately controlled with metformin alone. A population with such broad baseline characteristics is well suited for this investigation.

Table: Baseline characteristics.

<table>
<thead>
<tr>
<th>Clinical demographics</th>
<th>Total population (N=1997)</th>
<th>Age, years</th>
<th>56.9 (13.8, 50.0-89.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td>549 (27.5)</td>
<td>Female</td>
<td>549 (27.5)</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>94.8 (49.4, 69.3, 121.2)</td>
<td>BMI, kg/m²</td>
<td>31.7 (27.4, 32.7, 38.7)</td>
</tr>
<tr>
<td>Diabetes duration, years</td>
<td>7.2 (5.5, 6.3, 8.0)</td>
<td>A1C, %</td>
<td>8.2 (6.5, 5.3, 14.3)</td>
</tr>
<tr>
<td>A1C, mmol/mol</td>
<td>65.8 (57.6, 44.3, 139.3)</td>
<td>Fasting plasma glucose, mmol/L</td>
<td>5.5 (2.8, 14.0, 29.3)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>131.3 (141.0, 120.0, 202.0)</td>
<td>Diastolic blood pressure, mmHg</td>
<td>79.8 (69.3, 70.0, 121.0)</td>
</tr>
<tr>
<td>Pulse, beats/min</td>
<td>75.3 (68.3, 56.0, 110.0)</td>
<td>HbA1c, %</td>
<td>5.7 (5.3, 5.7, 6.0)</td>
</tr>
<tr>
<td>HbA1c, mmol/mol</td>
<td>47.5 (44.5, 44.0, 50.1)</td>
<td>Total cholesterol, mg/dL</td>
<td>176.9 (165.5, 133.5, 203.1)</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>61.5 (55.4, 66.0, 71.0)</td>
<td>LDL cholesterol, mg/dL</td>
<td>44.1 (35.0, 38.5, 53.1)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>167.2 (128.5, 32.1, 292.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Supported By: Novo Nordisk

Clinical Diabetes/Therapeutics POSTERS

1083-P Semaglutide Reduces Body Weight vs. Dulaglutide across Baseline BMI Subgroups in SUSTAIN 7

ADIE VILJEN, MATTHIAS BLUHER, FRANCIS C.C. CHOW, CAREL LE ROUX, JULIO ROSENSTOCK, NANNNA L. LAUSVIG, ILDIKO LINGVAY, Stevenage, United Kingdom, Leipzig, Germany, Hong Kong, China, Dublin, Ireland, Dallas, TX, Sabborg, Denmark

Semaglutide, a new GLP-1 analog for the treatment of T2D, showed significant and clinically meaningful reductions in HbA1c, and body weight (BW) across the SUSTAIN clinical trial program. SUSTAIN 7 compared semaglutide vs. dula-
Semaglutide Consistently Reduces Cardiovascular Events in Both Male and Female Subjects with Type 2 Diabetes

IRENE HRAMIAK, CYRUS DESOUZA, JOCHEN SEUFERT, THOMAS HANSEN, DESIRÉE THIELKE, ILDIKO LINGVAY, London, ON, Canada, Omaha, NE, Freiburg, Germany, Søborg, Denmark, Dallas, TX

Semaglutide is a new GLP-1 analog for the once-weekly treatment of T2D. In the SUSTAIN 6 CV outcomes trial, subcutaneous semaglutide (0.5 mg and 1.0 mg) added to standard of care significantly reduced major adverse CV events (MACE: non-fatal MI, non-fatal stroke or CV death) vs. placebo over 2 years in subjects with T2D at high CV risk. This post-hoc analysis assessed whether this CV risk reduction was consistent in male and female subjects.

Overall, 2,002 male and 1,295 female subjects were randomized. MACE was reported by fewer subjects with semaglutide vs. placebo in both sexes (p=0.45 for interaction); HR estimates were 0.68 (95% CI 0.50;0.92) in males, 0.84 (95% CI 0.54;1.31) in females and 0.74 (95% CI 0.58;0.95) in the overall study population. Overall, the pattern was similar across the individual MACE components (Table 1).

AEs were reported by similar proportions of males and females across treatments. The most frequent AEs reported were gastrointestinal, with higher rates in females than in males. The proportions of subjects prematurely discontinuing treatment due to AEs were comparable for males and females (Table 1). MACE and its components was reported in consistent proportions of males and females, and generally lower with semaglutide vs. placebo regardless of sex. The HR estimates for MACE with semaglutide vs. placebo for males and females were consistent with that of the overall study population.

In conclusion, BW reductions were greater with semaglutide vs. dulaglutide regardless of baseline BMI, consistent with findings in SUSTAIN 1-5 assessing semaglutide vs. comparators. AEs were reported by similar proportions of males and females across treatments. The most frequent AEs were gastrointestinal, with higher rates in females than in males. The proportions of subjects prematurely discontinuing treatment due to AEs were comparable for males and females (Table 1).

MACE and its components was reported in consistent proportions of males and females, and generally lower with semaglutide vs. placebo regardless of sex. The HR estimates for MACE with semaglutide vs. placebo for males and females were consistent with that of the overall study population.

Supported By: Novo Nordisk

Table 1. Major adverse cardiovascular events (MACE: non-fatal myocardial infarction, non-fatal stroke or cardiovascular death) and adverse events by sex in the SUSTAIN 6 trial.

<table>
<thead>
<tr>
<th></th>
<th>Semaglutide (pooled 0.5 mg and 1.0 mg)</th>
<th>Placebo (pooled 0.5 mg and 1.0 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>MACE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>75 (1.7)*</td>
<td>103 (1.4)*</td>
</tr>
<tr>
<td>Female</td>
<td>35 (1.5)*</td>
<td>42 (0.9)*</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>32 (1.3)</td>
<td>48 (0.9)</td>
</tr>
<tr>
<td>Female</td>
<td>15 (2.4)</td>
<td>16 (2.4)</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18 (1.8)</td>
<td>27 (2.7)</td>
</tr>
<tr>
<td>Female</td>
<td>5 (1.3)</td>
<td>12 (2.4)</td>
</tr>
<tr>
<td>CV death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>30 (2.0)</td>
<td>24 (2.4)</td>
</tr>
<tr>
<td>Female</td>
<td>14 (2.2)</td>
<td>11 (1.8)</td>
</tr>
<tr>
<td>Other safety outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any AE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>888 (88.2)</td>
<td>879 (89.1)</td>
</tr>
<tr>
<td>Female</td>
<td>566 (89.1)</td>
<td>574 (87.4)</td>
</tr>
<tr>
<td>Serious AE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>327 (32.5)</td>
<td>357 (36.2)</td>
</tr>
<tr>
<td>Female</td>
<td>177 (27.9)</td>
<td>217 (33.0)</td>
</tr>
<tr>
<td>Severe AE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>233 (23.6)</td>
<td>238 (24.1)</td>
</tr>
<tr>
<td>Female</td>
<td>173 (26.1)</td>
<td>128 (19.3)</td>
</tr>
<tr>
<td>All leading to premature treatment discontinuation</td>
<td>126 (12.5)</td>
<td>70 (7.1)</td>
</tr>
<tr>
<td>Male</td>
<td>88 (12.5)</td>
<td>40 (6.1)</td>
</tr>
<tr>
<td>Female</td>
<td>37 (12.5)</td>
<td>30 (12.0)</td>
</tr>
<tr>
<td>Gastrointestinal AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>498 (48.8)</td>
<td>336 (32.0)</td>
</tr>
<tr>
<td>Female</td>
<td>313 (39.5)</td>
<td>234 (22.7)</td>
</tr>
</tbody>
</table>

*P values were calculated using the Mantel-Haenszel test. CV events are defined as non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death. BMI was calculated as weight (kg) divided by height (m) squared. HRs were calculated using a Cox proportional hazards model with adjustment for age, sex, BMI, randomization group, the LDL-C level at entry, the subject's smoking status, and baseline vital signs. The risk estimates presented are those for the overall study population.
Compared with the BP group. The mean BG, SD, coefficient of variation, and percentage of BG >240 and BG <70 was significantly lower in the BP+DU (%hIGR), mean BG, glucose variability (GV), and insulin dose.

We compared the percentage of hIGR with all measured BGs within 100-180 mg/dL, we define this range as the hospitalized ideal glucose assignment. Because we consider the ideal BG during hospitalization to be cose (BG) levels before and after every meal were measured for 7 days after BP+DU therapy, those receiving BP therapy combined with DU. Blood glucose levels after basal insulin and corrective doses of regular insulin before meals, or

Participants were randomized to either basal-plus (BP) therapy, those receiving BP therapy combined with DU. Therapeutic strategies targeting the incretin system are effective in treating type 2 diabetes. GLP-1 receptor agonists (GLP-1RA) reduce post-prandial glucose levels by stimulating insulin and inhibiting glucagon release, but also by reducing gastric motility. Although GLP-1RA reduce gastric motility initially, their ability to sustain this over the long-term is reduced and the mechanism(s) underlying this change is not known. GLP-1R are expressed in neurons of the nucleus of the solitary tract (NTS) that play a fundamental role in regulating metabolism and gastric motility. Here, we examined whether long-term use of GLP-1RA alters GLP-1R expression in the NTS that can influence gastric motility. C57BL6 mice were treated with either saline, lixisenatide, liraglutide or exenatide ER, for 2hrs, 1d, 1wk, 2wks, 4wks or 6wks before their effects on gastric motility and NTS GLP-1R mRNA expression were evaluated. All GLP-1RA effectively slowed gastric emptying in the early stages of treatment, but within 1-2wks, their efficacy waned. By 4-6wks, no significant reduction in gastric motility was observed with any of the treatments, except in the group treated with exenatide ER, which showed a significant reduction in gastric motility and NTS GLP-1R mRNA expression. These findings suggest that the decrease in gastric motility observed with GLP-1RA is not due to a direct effect on gastric motility but rather to a decrease in NTS GLP-1R expression. Therefore, the decrease in gastric motility observed with GLP-1RA is likely to be due to a direct effect on gastric motility but rather to a decrease in NTS GLP-1R expression. Therefore, the decrease in gastric motility observed with GLP-1RA is likely to be due to a decrease in NTS GLP-1R expression. Therefore, the decrease in gastric motility observed with GLP-1RA is likely to be due to a decrease in NTS GLP-1R expression.

**Table.**

<table>
<thead>
<tr>
<th>Group</th>
<th>n=9/4, N=27</th>
<th>n=69/9, N=27</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>70.1±14</td>
<td>70.9±13</td>
<td>0.822</td>
</tr>
<tr>
<td>Male, N (%)</td>
<td>18 (67)</td>
<td>15 (56)</td>
<td>0.577</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.6±5.7</td>
<td>25.1±6.7</td>
<td>0.904</td>
</tr>
<tr>
<td>Duration, years</td>
<td>10.1±8.8</td>
<td>8.7±9.4</td>
<td>0.488</td>
</tr>
<tr>
<td>Hba1C, %</td>
<td>8.0±1.9</td>
<td>8.2±1.7</td>
<td>0.401</td>
</tr>
<tr>
<td><strong>Frequency of the measured BGs in each BG ranges, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BG &lt;70</td>
<td>21 (2.3)</td>
<td>4 (0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BG 70-100</td>
<td>57 (7.7)</td>
<td>99 (10)</td>
<td>0.019</td>
</tr>
<tr>
<td>BG 100-180 (%hIGR)</td>
<td>399 (44)</td>
<td>545 (56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BG &gt;180</td>
<td>184 (21)</td>
<td>82 (8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BG &lt;70 &amp; BG &gt;180</td>
<td>121 (13)</td>
<td>54 (6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Daily BG profiles, mean±SD mg/dL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>131±38</td>
<td>127±40</td>
<td>0.254</td>
</tr>
<tr>
<td>After breakfast</td>
<td>244±61</td>
<td>196±54</td>
<td>0.004</td>
</tr>
<tr>
<td>Before lunch</td>
<td>216±65</td>
<td>173±56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>After lunch</td>
<td>195±62</td>
<td>182±54</td>
<td>0.041</td>
</tr>
<tr>
<td>Evening</td>
<td>135±47</td>
<td>143±44</td>
<td>0.232</td>
</tr>
<tr>
<td>After dinner</td>
<td>203±62</td>
<td>177±54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Glucose variability, mean±SD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Individual glucose SD during study</td>
<td>62.5±21</td>
<td>45.0±14</td>
<td>0.001</td>
</tr>
<tr>
<td>Individual glucose CV during study</td>
<td>0.34±0.09</td>
<td>0.27±0.05</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Hypoglycemic event, N (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients &lt;70 mg/dL</td>
<td>9 (33)</td>
<td>3 (11)</td>
<td>0.099</td>
</tr>
<tr>
<td>Insulin therapy, mean±SD U/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total insulin</td>
<td>17.1±6.6</td>
<td>16.1±6.4</td>
<td>0.782</td>
</tr>
<tr>
<td>Total glargine insulin</td>
<td>12.0±5.7</td>
<td>12.5±4.8</td>
<td>0.55</td>
</tr>
<tr>
<td>Total regular insulin</td>
<td>5.4±2.5</td>
<td>3.6±2.8</td>
<td>0.017</td>
</tr>
</tbody>
</table>

**Conclusion:** There is enough information to discard the concern regarding GLP-1 agonists and pancreatic cancer.

**Figure 1. Forest Plot for pancreatic cancer in GLP-1 analogs vs. control**

**Figure 2. TSA for pancreatic cancer**

---

**1088-P**

**Long-Term Use of GLP-1 Receptor Agonists Alter GLP-1 Receptor mRNA Expression in Hindbrain Pathways That Regulate Gastric Motility in Mice**

**PEILI WANG, RAMANAIH MAMILLAPALLI, WANLING ZHU, OWEN CHAN,** **New Haven, CT, Salt Lake City, UT**

Therapeutic strategies targeting the incretin system are effective in treating type 2 diabetes. GLP-1 receptor agonists (GLP-1RA) reduce post-prandial glucose levels by stimulating insulin and inhibiting glucagon release, but also by reducing gastric motility. Although GLP-1RA reduce gastric motility initially, their ability to sustain this over the long-term is reduced and the mechanism(s) underlying this change is not known. GLP-1R are expressed in neurons of the nucleus of the solitary tract (NTS) that play a fundamental role in regulating metabolism and gastric motility. Here, we examined whether long-term use of GLP-1RA alters GLP-1R expression in the NTS that can influence gastric motility. C57BL6 mice were treated with either saline, lixisenatide, liraglutide or exenatide ER, for 2hrs, 1d, 1wk, 2wks, 4wks or 6wks before their effects on gastric motility and NTS GLP-1R mRNA expression were evaluated. All GLP-1RA effectively slowed gastric emptying in the early stages of treatment, but within 1-2wks, their efficacy waned. By 4-6wks, no significant reduction in gastric motility was observed with any of the agonists. Of note, we observed a decline in GLP-1R mRNA expression in the NTS at 1-2wks of treatment which corresponded to the initial decline in drug efficacy. At 4wks, however, GLP-1R mRNA levels returned to pretreatment levels and suppression of gastric motility was no longer observed. To test whether the decrease in NTS GLP-1R expression contributed to attenuating the suppressive effects on gastric motility, we knocked down GLP-1R expression in the NTS using an adeno-associated viral vector to express a shRNA against the GLP-1R. Reducing NTS GLP-1R expression prevented the suppressive effects of lixisenatide on gastric motility, suggesting in mice, a decrease in NTS GLP-1R expression may contribute to the initial decrease in
A1C Target Attainment in Patients with T2D Receiving iGlarLixi Who Reach PPG and FPG Targets in the Lixilan-I Trial

LAWRENCE A. LEITER, JASON CHAO, ARAMESH SAREMI, TERRY A. DEX, JAIME A. DAVIDSON NV, Toronto, ON, Canada, Bridgewater, NJ, Pluckemin, NJ, Dallas, TX

Treatments that reduce A1C levels often do not reflect improvements in both fasting and postprandial hyperglycemia. Data from T2D patients (n=363) with T2D uncontrolled on basal insulin + DAs in the Lixilan-I trial (NCT02058160) were used to investigate the association between achieving PPG/PPG targets and A1C target attainment after 30 weeks of treatment with iGlarLixi (n=366) or iGlar (n=365). Outcomes were A1C target attainment, A1C change from baseline, and mean A1C at Week 30 in pts achieving both FPG and PPG target, FPG target only, PPG target only, or neither, using ADA glycaemic targets. The proportion of pts reaching PPG only, or both FPG and PPG target, was numerically higher for iGlarLixi, while the proportion reaching FPG target only was numerically higher for iGlar (Figure 1A). iGlarLixi-treated pts reaching both FPG and PPG targets, or PPG target only, showed statistically significant greater A1C changes from baseline, lower end-of-trial A1C, and a higher proportion reaching A1C target than iGlar-treated pts (Figure 1B-D). Despite a numerically higher proportion of pts reaching FPG target only in the iGlar arm, A1C outcomes were in favor of pts receiving iGlarLixi.

In conclusion, the complementary actions of iGlarLixi on both fasting and postprandial hyperglycemia were associated with better A1C target attainment compared with iGlar alone, which mainly targets fasting hyperglycemia.

Investigations into Tissue Distribution and Inhibition of Food Consumption with Efpeglenatide

YOUNG JIN PARK, IN YOUNG CHOI, MICHAEL E. TRAUTMANN, MARCUS HOMPESCH, CHRISTOPHER H. SORLI, Seoul, Republic of Korea, Chula Vista, CA, Bridgewater, NJ

Efpeglenatide (efpeg), a long-acting glucagon-like peptide-1 receptor agonist in development for type 2 diabetes, induces weight loss through satiety and reduced food intake. Studies in Sprague Dawley rats investigated how peripheral and central mechanisms contribute to the anorectic effects of efpeg. Tissue distribution of efpeg was assessed by whole-body autoradioluminography with 14C-efpeg. The contribution of vagal nerve signaling to food intake control was assessed in vagotomized rats treated with exenatide (0.15 or 0.45 nmol/kg twice daily) or efpeg (0.71 or 2.1 nmol/kg every 2 days). Pharmacokinetic parameters and mean radioactivity of 14C-efpeg in selected organs/tissues are shown in Figure. Peak concentration (Cmax) of 14C-efpeg was highest in the kidney cortex, Cmax at all other sites was similar to lower than in blood, relatively high in the intestine and pituitary, with below-quantifiable levels in the cerebellum/cerebrum. Inhibition of food intake was not attenuated in vagotomized vs. sham-operated rats at higher doses of efpeg (3-day cumulative intake: 47.4 vs. 49.4 g) or exenatide (54.9 vs. 60.7 g), suggesting a non-vagal mechanism for these anorectic effects. These findings suggest that central mechanisms are involved in the anorectic effects of efpeg in this animal model; potential cell-signaling effects of efpeg in the intestine and pituitary need to be investigated further.

In Vitro Studies to Evaluate the Receptor Kinetics of Efpeglenatide vs. Other Glucagon-Like Peptide-1 Receptor (GLP-1R) Agonists

IN YOUNG CHOI, MJ JIN MOON, MICHAEL E. TRAUTMANN, MARCUS HOMPESCH, CHRISTOPHER H. SORLI, Seoul, Republic of Korea, Chula Vista, CA, Bridgewater, NJ

Efpeglenatide (efpeg), a long-acting glucagon-like peptide-1 receptor agonist in development for the treatment of T2D. Efpeg's effects on the GLP-1 R suggest that it is a superagonist: a ligand that leads to greater maximal signaling and stimulation compared with its endogenous ligand. In vitro studies investigated the superagonistic effects of efpeg compared to the effects of liraglutide (lira) and dulaglutide (dula) (Figure). The superagonistic effect of efpeg on GLP-1 R may be due to its specific binding characteristics, allowing more cell-surface receptor availability for intracellular signaling. The clinical relevance of these findings should be assessed further.
Effects of IDegLira (Insulin Degludec/Liraglutide) in Patients with Poorly Controlled Type 2 Diabetes (T2D) with A1C >9%—Analyses from the DUAL Program

DANNY SUGIMOTO, JUAN P. FRIAS, DIDIER GOURIOT, ROBERT TAKACS, TING JIA, PETRA ORSY, STEPHEN C. BAIN, Chicago, IL; Los Angeles, CA; La Rochelle, France; Szeged, Hungary; Seborg, Denmark; Swansea, United Kingdom

Despite a variety of treatment options for type 2 diabetes (T2D), more than half of patients do not achieve glycemic control. In a post-hoc analysis of the DUAL I (oral antidiabetic drugs [OADs]), II, IV, and VII (basal insulin + OADs) trials, we evaluated patients with an A1C >9% at baseline to determine the impact of IDegLira on their glycemic control. Within each DUAL trial, baseline characteristics for patients with A1C >9% were similar for all treatment groups. In DUAL I, II and VII, treatment with IDegLira resulted in greater reductions in A1C from baseline, vs. comparators of basal insulin or liraglutide, leading to lower A1C at end of trial (EOT). In DUAL VII, reduction in A1C from baseline and A1C at EOT were comparable for IDegLira and insulin glargine U100 (100 U/mL) + insulin aspart (<4 times/day). At EOT, the composite endpoint of A1C <7% without hypoglycemia (DUAL I, II and VII; unable to self-treat and or plasma glucose [PG] <56 mg/dL, DUAL VII: unable to self-treat or PG <56 mg/dL with hypoglycemia symptoms) was achieved by a greater proportion of patients treated with IDegLira than with comparators.

In conclusion, even in patients with T2D with A1C >9%, IDegLira treatment achieved glycemic control with a high proportion of patients achieving A1C <7% and clinically important composite endpoints of A1C <7% without hypoglycemia and/or weight gain.

Table.

Change in A1C, A1C at EOT and % patients achieving composite endpoints at EOT for patient group with baseline A1C >9% from DUAL I, II, IV and VII

<table>
<thead>
<tr>
<th>Trial</th>
<th>A1C at Baseline</th>
<th>% Achieving A1C &lt;7% without Hypoglycemia*</th>
<th>% A1C at EOT</th>
<th>% Achieving A1C &lt;7% with Hypoglycemia* or Weight Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>DUAL I (NCT 01330023)</td>
<td>8.7</td>
<td>6.9</td>
<td>7.7</td>
<td>7.3</td>
</tr>
<tr>
<td>DUAL II (NCT 01330023)</td>
<td>7.6</td>
<td>5.4</td>
<td>6.0</td>
<td>5.7</td>
</tr>
<tr>
<td>DUAL IV (NCT 01330023)</td>
<td>8.3</td>
<td>7.8</td>
<td>8.5</td>
<td>8.1</td>
</tr>
<tr>
<td>DUAL VII (NCT 02000202)</td>
<td>8.1</td>
<td>7.5</td>
<td>7.3</td>
<td>7.1</td>
</tr>
</tbody>
</table>

*To the last 12 weeks of treatment. In DUAL II, maximum allowed dose of liraglutide was 100 μg. Hypoglycemia definition: subject unable to self-treat and/or a recorded plasma glucose <2.2 mmol/L (<40 mg/dL) (DUAL I, II and VII); subject unable to self-treat or a recorded plasma glucose <3.9 mmol/L (<70 mg/dL) with symptoms consistent with hypoglycemia (DUAL VII). Δ: change; A1C: glycated hemoglobin; EOT: end of trial; U100: insulin aspart; IDegLira, insulin degludec/liraglutide; PLH, without.

Supported By: Novo Nordisk A/S

Impact of Type 2 Diabetes (T2D) Duration on Response to iGlarLixi vs. IGLAR—A Subanalysis of LixiLan-L

LAWRENCE BLONDE, LORI BERNARD, ARAMESH SAREMI, YAO HUANG, VANITA ARODA, DENIS RACCAH, New Orleans, LA; Winnipeg, MB, Canada; Pluckemin, NJ; Somerset, NJ; Hollywood, MD; Marseille, France

Shorter-acting GLP-1RA like lixisenatide have insulin-independent effects, which may benefit patients (pts) with longer T2D duration and more β-cell dysfunction. We assessed the effects of insulin glargine (iGlar) vs. fixed-ratio iGlar plus lixisenatide (iGlarLixi) by T2D duration in the LixiLan-L trial (N=736). HbA1c, weight, insulin dose change (BL-Wk 30) and hypoglycemia were analyzed in pts divided in quartiles by recorded baseline (BL) T2D duration (<7.3, 7.3-10.7, 10.7-15.7, >15.7 years). Pts were also grouped by BL insulin dose (may relate inversely to β-cell function). BL HbA1c was higher in long-duration quartiles but similar with iGlarLixi vs. iGlar. iGlarLixi reduced HbA1c more vs. iGlar across duration quartiles (Figures). Difference was greater in pts in the longest duration quartile (LS mean difference [SE] -0.62 [0.13]; p<0.0001). In both treatment groups, pts in the shortest duration quartile had the greatest insulin dose change (BL-Wk 30). Difference in hypoglycemia (iGlarLixi vs. iGlar) was greatest in pts in the longest duration quartile (LS 3.3 vs. 6.9 events/pt-yr; p<0.0001). In pts grouped by T2D duration and insulin dose, those with both long duration (>15.7 years) and high dose (>42 U) showed greatest difference in HbA1c lowering with iGlarLixi vs. iGlar. In LixiLan-L, iGlarLixi lowered HbA1c more vs. iGlar regardless of T2D duration, with greatest difference in those with longest duration.

Supported By: Sanofi U.S.

Glycemic Target Attainment in Insulin-Naïve Patients with T2D Receiving iGlarLixi

CYRUS DESOUZA, VIVAN FORSEDA, JUAN P. FRIAS, LUC VAN GAAL, FRANCESCO GIORGINO, JASON CHAO, TERRY A. DEX, MICHELLE ROBERTS, ARAMESH SAREMI, LAWRENCE A. LEITER, OMAR ALI, LA JOLLA, CA; Antwerp, Belgium; Bari, Italy; Bridgewater, NJ; Readington, NJ; Pluckemin, NJ; Toronto, ON, Canada

This study assessed the relationship between FPG, PPG and glycated hemoglobin (A1C) target attainment using ADA glycemic targets in patients (pts) with T2D. A post-hoc analysis of the phase 3 LixiLan-A (NCT03058147) trial assessed the efficacy and safety of iGlarLixi (n=468) vs. insulin glargine U100 (iGlar) (n=468) and lixisenatide (Lixi) (n=233) in pts uncontrolled on metformin and/or GLP-1RA, reducing more on metformin, over a 30-week period. The proportion of pts reaching both FPG and PPG target was highest for iGlarLixi, while the proportions of those reaching FPG or PPG targets only were highest for iGlar (targeting FPG) and Lixi (targeting PPG), respectively (Figure 1A). There was a stepwise trend in A1C change, end-of-study A1C, and proportion of pts reaching A1C goals in favor of iGlarLixi, followed by iGlar and Lixi (Figure 1B-D). Pts reaching both FPG and PPG targets had the greatest A1C drop and lowest A1C values, and represented the largest proportion of pts achieving A1C target. No differences were observed in hypoglycemia rates in all treatment arms, and a greater proportion of pts experienced weight loss with iGlarLixi vs. iGlar (55.3% vs. 39.3%). By simultaneously targeting fasting and postprandial hyperglycemia, iGlarLixi treatment results in greater A1C reduction and better A1C target attainment than iGlar or Lixi alone.

Supported By: Novo Nordisk A/S

ADA-Supported Research

Moderrated Poster Discussion
Diabetes and Endocrinology clinics. Patients completed questionnaires assessing medication and device satisfaction and medication adherence at baseline and at follow-up (3-6 months). Standard clinical outcomes were collected. To date, 320 subjects have been enrolled: 187 dulaglutide (DULA), 110 liraglutide (LIRA), and 23 switching from LIRA to DULA. At baseline, PRO’s and clinical measures were similar between cohorts (mean age 54.2 ± 10.1 years; mean HbA1c 8.4 ± 1.5%). In this interim analysis of 110 completers to date (mean follow-up 3.3 months), there was a trend for the 77 DULA completers to have greater improvements in PRO scores compared to the 33 LIRA completers (Figure). To-date, DULA subjects had a 1.1 ± 0.9% reduction in HbA1c and 2.2 ± 3.3 kg reduction in weight. The LIRA subjects showed similar trends (1.2 ± 1.0% reduction in HbA1c and 2.4 ± 3.2 kg reduction in weight). Interim analysis of this real-world, specialist-led registry of patients initiating GLP-1 RA therapy showed similar improvements in PRO’s and clinical outcomes.
Preclinical Effects of Efpeglenatide, a Long-Acting Glucagon-Like Peptide-1 Receptor Agonist, Compared with Liraglutide and Dulaglutide

MICHAEL E. TRAUTMANN, IN YOUNG CHOI, JUNG KUK KIM, CHRISTOPHER H. SORLI, OHLA VISTA, CA, SEOUL, Republic of Korea, Bridgewater, NJ

Efpeglenatide (efpeg) is a long-acting glucagon-like peptide-1 receptor agonist (GLP-1 RA) in development for type 2 diabetes. The effects of efpeg vs. those of liraglutide (lira) and dulaglutide (dula) on glucodynamics and weight/lipid profiles were studied over 4 weeks in mouse models of diabetes (db/db) and obesity (diet-induced obesity [DIO]), respectively.

Results: Several co-agonists show enhanced maximal insulin release (vs. other GLP-1 RAs in mice). These effects may be due to the variable bias at the GLP-1R.

In summary, in a real-world setting, few patients treated with GLP-1RA achieved good glycemic control after stopping insulin. Baseline insulin dose was the main baseline predictor of successful ID.

Table. Characteristics of Patients According to Insulin Discontinuation at 6 Months. Data are Percentage, Mean (SD), Median (IQR) or Mean Difference (univariate vs. multivariate analyses).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Discontinuation</th>
<th>No Discontinuation</th>
<th>Between-group Difference (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>exenatide BID (%)</td>
<td>41.9</td>
<td>21.1</td>
<td>0.044</td>
</tr>
<tr>
<td>liraglutide (%)</td>
<td>51.6</td>
<td>64.1</td>
<td></td>
</tr>
<tr>
<td>exenatide GLN (%)</td>
<td>6.5</td>
<td>14.8</td>
<td>GP(150)</td>
</tr>
<tr>
<td>women (%)</td>
<td>74.2</td>
<td>52.3</td>
<td>0.028</td>
</tr>
<tr>
<td>age (y)</td>
<td>59.3 (10.8)</td>
<td>62.5 (10.9)</td>
<td>0.11</td>
</tr>
<tr>
<td>duration of T2DM (y)</td>
<td>11.5 (9.6-13)</td>
<td>16.4 (10.4-22.9)</td>
<td>0.002</td>
</tr>
<tr>
<td>duration of insulin therapy (y)*</td>
<td>2.3 (0.9-3.9)</td>
<td>5.7 (2.6-12.1)</td>
<td>0.011</td>
</tr>
<tr>
<td>insulin dose (U/d)</td>
<td>31.2 (13.9)</td>
<td>61.8 (41.4)</td>
<td>-0.001</td>
</tr>
<tr>
<td>metformin (%)</td>
<td>80.6</td>
<td>84.4</td>
<td>0.614</td>
</tr>
<tr>
<td>sulfonylureas (%)</td>
<td>48.4</td>
<td>28.9</td>
<td>0.038</td>
</tr>
<tr>
<td>glitazones (%)</td>
<td>16.1</td>
<td>6.3</td>
<td>0.072</td>
</tr>
<tr>
<td>DPP-4 inhibitors (%)</td>
<td>22.6</td>
<td>34.4</td>
<td>0.207</td>
</tr>
<tr>
<td>diabetic renal disease (%)</td>
<td>9.7</td>
<td>38.3</td>
<td>0.002</td>
</tr>
<tr>
<td>baseline A1C (%)</td>
<td>7.87 (1.36)</td>
<td>8.33 (1.39)</td>
<td>0.036</td>
</tr>
<tr>
<td>A1C reduction (%) at 6 months**</td>
<td>-0.23 (0.85; -0.8)</td>
<td>-1.19 (1.2; -0.84)</td>
<td>0.011</td>
</tr>
<tr>
<td>A1C&lt;7% at 6 months (%)</td>
<td>15.9</td>
<td>26.4</td>
<td>0.974</td>
</tr>
<tr>
<td>baseline weight (kg)</td>
<td>97.4 (23.0)</td>
<td>95.3 (16.5)</td>
<td>0.546</td>
</tr>
<tr>
<td>weight loss (kg) at 6 months**</td>
<td>-5.9 (7.4; -13.9)</td>
<td>-7.4 (2.6)</td>
<td>0.060</td>
</tr>
<tr>
<td>hypoglycemia (%)</td>
<td>22.6</td>
<td>33.6</td>
<td>0.236</td>
</tr>
</tbody>
</table>

GLP-1RA withdrawal (%)     | 6.5            | 17.2               | 0.134                        |

Supported By: Hammi Pharm. Co., Ltd, Sandofi

Effect of Biased GLP-1/Glucagon Receptor Co-agonists on Insulin Secretion

GALA FAROOQ, BEN JONES, JAMES S. MINNION, STEPHEN R. BLOOM, London, United Kingdom

Introduction: The effect of dual GLP-1 and glucagon analogues on insulin secretion remains unclear. Here, we investigated the effect of novel GLP-1/glucagon receptor (GLP-1R/GCGR) co-agonists on beta cell lines, finding augmented insulin release compared to reference agonist Exendin-4. This effect was related to signalling bias at the GLP-1R.

Methods: GLP-1R/GCGR co-agonists were designed, based on the sequence of oxyntomodulin. INS-1 832/3 beta cells and MIN6B1 beta cells were used to perform 24 hour insulin secretion assays. Ligand-directed signal bias was determined from cyclic adenosine monophosphate (cAMP) and β arrestin-1/2 responses measured by enzyme fragment complementation in CHO-K1 cells expressing GLP-1R or GCGR.

Results: Several co-agonists showed enhanced maximal insulin release compared to Exendin-4 (representative co-agonist Pep A vs. Exendin-4 fold insulin release, normalized to 11mM glucose: INS-1 823/3 cells 4.45 ± 0.24
vs. 2.55±0.22, p=0.0002; MINDB1 cells 2.28±0.22 vs. 1.57±0.08, p=0.002).
At the GLP-1 receptor, co-agonists were biased towards CAMP generation, compared to the β arrestin-2 pathway (delta log (v/K_i) -0.70 ± 0.11 [Peptide A], vs. 0.23 ± 0.11 [Exendin-4], p<0.0001). As the GGR, no significant change in bias was seen relative to native glucagon.

Conclusion: GLP-1R/GCCR co-agonists show enhanced insulin release in vitro compared to exendin-4. As canonical effects of β arrestin recruitment include desensitisation and loss of cell surface receptors via endocytosis, the observed signal bias with these peptides may be linked to their insulino- tropic effect. These findings may inform the design of more potent insulino- tropic compounds for therapeutic use in type 2 diabetes.

1101-P
Dulaglutide Has Favorable Outcomes in Elderly or Renal Impairment Patients with Type 2 Diabetes
SHIZUKA KANÉKO, YUGUÉI UEDE, YUMIKO TAHARA, Takatsu, Japan

In Japan, society is aging. Additionally, dialysis is performed in one out of 400 people. Safe, effective and convenient therapies for elderly or renal impairment type 2 diabetic patients (T2D) including those undergoing dialysis are needed. We investigated the the long-term efficacy and safety of a new once weekly GLP-1R agonist dulaglutide (Dura) on glycemic control in those. We conducted two different retrospective analyses of 2 year efficacy and safety of Dura in T2D according to; 1) subgroups stratified by ages (≥70 years old or >71 years old), 2) renal impairment including those undergoing dialysis. Regarding 1) Of 322 T2D, 214 elderly T2D (109 males, 76.8±9.9 years old, disease duration of 7.6±7.4 years, HbA1c 8.3±1.8%, BMI 24.1±1.1) and 108 younger T2D (48 males, 58.4±10.6 years old, disease duration of 5.6±6.5 years, HbA1c 7.9±1.4%, BMI 25.5±4.4) were newly administered Dura weekly. Elderly and younger T2D treated with Dura achieved 7.0±6.9% and 7.2±6.9% in HbA1c after 2 years respectively. 20 elderly T2D registered Dura weekly. Elderly and younger T2D treated with Dura achieved 7.0±6.9% and 7.2±6.9% in HbA1c after 2 years respectively. 20 elderly T2D

1102-P
Exploring Two Dose Regimens of ITCA 650 to Switch from Stable Liraglutide Therapy in Type 2 Diabetes (T2D)
NEDA RASOULI, JULIO RIGENSTOCK, SAMER NAKHE, BRIAN SCHWARTZ, PRAKASH PRABHAKAR, SYDNEY L. KRUGER, HOLLY HUANG, MICHELLE A. BARON, Denver, CO, Dallas, TX, Las Vegas, NV, Boston, MA, Monistone, NJ

ITCA 650 is an investigational titanium osmotic mini pump that is subdermally placed in the abdominal wall during a brief office procedure. As an investigational product for the treatment of type 2 diabetes (T2D), ITCA 650 provides a continuous subcutaneous infusion of exenatide over 3 or 6 months. An integrated analysis of efficacy and safety was conducted from 2 double-blind, randomized, Phase 3 studies, which evaluated pooled data with results observed from individual Phase 3 studies, which demonstrated patients in each group discontinued for TEAEs. The results are consistent with results observed from individual Phase 3 studies, which demonstrated that ITCA 650 is effective for lowering HbA1c and weight, for achieving a complication. It might also be expected to improve QoL of patients due to a reduced burden when taking medicines daily or hypoglycemia, and due to saving care person’s burden in elderly society which is workforce shortage, result in reduce of medical costs.

Table. Baseline Characteristics and Clinical Outcomes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ITCA 650 20/60 mcg/d</th>
<th>Placebo or sitagliptin 100 mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>55.1±9.7</td>
<td>54.7±9.1</td>
</tr>
<tr>
<td>Baseline HbA1c, %</td>
<td>7.7±0.3</td>
<td>7.7±0.9</td>
</tr>
<tr>
<td>Baseline weight, kg</td>
<td>94.2±19.6</td>
<td>98.2±21.9</td>
</tr>
<tr>
<td>Weight change, %</td>
<td>5.3±2.5</td>
<td>-1.3±0.5</td>
</tr>
<tr>
<td>HbA1c change, %</td>
<td>-1.4±0.06</td>
<td>0.0±0.15</td>
</tr>
<tr>
<td>BMI decrease, %</td>
<td>15.2±3.0</td>
<td>17 (11%)</td>
</tr>
<tr>
<td>Waist decrease, %</td>
<td>15.5±3.0</td>
<td>17 (11%)</td>
</tr>
<tr>
<td>Waist to Hip ratio decrease, %</td>
<td>11 (7.5%)</td>
<td>16 (10.5%)</td>
</tr>
<tr>
<td>HbA1c decrease, %</td>
<td>-2 (1.5%)</td>
<td>17 (11%)</td>
</tr>
<tr>
<td>Nausea, %</td>
<td>2 (1.5%)</td>
<td>0.0%</td>
</tr>
<tr>
<td>Vomiting, %</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Glucagon, %</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>GI TEAEs</td>
<td>5.2%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

1. Mean ± standard deviation
2. All patients had high BMI; mean ± standard error of BMI was 30.8±4.0 kg/m²

1103-P
Efficacy and Safety of ITCA 650, an Injection-Free GLP-1RA, in T2D Patients—A Pooled Analysis of Phase 3 Studies
LISE L. KIERS, PRAKASH PRABHAKAR, BRIAN SCHWARTZ, HOLLY HUANG, MICHELLE A. BARON, BOSTON, MA, MONISTONE, NJ

ITCA 650 consists of a small titanium osmotic mini-pump that is subdermally placed in the abdominal wall during a brief office procedure. As an investigational product for the treatment of type 2 diabetes (T2D), ITCA 650 provides a continuous subcutaneous infusion of exenatide for 3 or 6 months. An integrated analysis of efficacy and safety was conducted from 2 double-blind, randomized, Phase 3 studies, which evaluated pooled data with results observed from individual Phase 3 studies, which demonstrated that ITCA 650 is effective for lowering HbA1c and weight, for achieving a composite of HbA1c/weight reduction and target HbA1c <7%, and is well tolerated.

Table. Baseline Characteristics, outcomes, and adverse events from pooled analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ITCA 20/60 mcg/d</th>
<th>Placebo or sitagliptin 100 mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>55.1±9.7</td>
<td>54.7±9.1</td>
</tr>
<tr>
<td>Baseline HbA1c, %</td>
<td>7.7±0.3</td>
<td>7.7±0.9</td>
</tr>
<tr>
<td>Baseline weight, kg</td>
<td>94.2±19.6</td>
<td>98.2±21.9</td>
</tr>
<tr>
<td>Weight change, %</td>
<td>5.3±2.5</td>
<td>-1.3±0.5</td>
</tr>
<tr>
<td>HbA1c change, %</td>
<td>-1.4±0.06</td>
<td>0.0±0.15</td>
</tr>
<tr>
<td>BMI decrease, %</td>
<td>15.2±3.0</td>
<td>17 (11%)</td>
</tr>
<tr>
<td>Waist decrease, %</td>
<td>15.5±3.0</td>
<td>17 (11%)</td>
</tr>
<tr>
<td>Waist to Hip ratio decrease, %</td>
<td>11 (7.5%)</td>
<td>16 (10.5%)</td>
</tr>
<tr>
<td>HbA1c decrease, %</td>
<td>-2 (1.5%)</td>
<td>17 (11%)</td>
</tr>
<tr>
<td>Nausea, %</td>
<td>2 (1.5%)</td>
<td>0.0%</td>
</tr>
<tr>
<td>Vomiting, %</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Glucagon, %</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>GI TEAEs</td>
<td>5.2%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

1. Mean ± standard deviation
2. All patients had high BMI; mean ± standard error of BMI was 30.8±4.0 kg/m²

1. Only within treatment group comparisons were performed. Between treatment group comparisons were not performed because placebo or sitagliptin was not used in both studies in this analysis.
2. Background therapy included various oral agents in FREEDOM-1 and metformin only in FREEDOM-2. Excluded post- rescue data.
3. p=0.05 vs. baseline. In conclusion, patients on stable liraglutide therapy can be switched to ITCA 650 60 mcg/d without the need for up-titration from a lower dose.
1105-P
Bone Protective Effect of a Novel Long-Acting GLP-1/GIP/Glucagon Tripeptide Agonist in an Animal Model

SANGDON LEE, YU-YON KIM, JONG SUK LEE, SANG HYUN LEE, YOUNG HOON KIM, IN YOUNG CHOI, SUN JIN KIM, SANGDON LEE, YU-YON KIM, JONG SUK LEE, SANG HYUN LEE, YOUNG HOON KIM, IN YOUNG CHOI, SUN JIN KIM, Seoul, Republic of Korea

Severe weight loss is often associated with reduction of bone mineral density (BMD) and an imbalance between bone formation and resorption in obese people. As a consequence, there can be an increased risk of bone fractures with body weight loss. Several studies have proposed that the gut hormones, GIP and GLP-1, might be modulators of bone growth and remodeling. HM15211 is a novel long-acting GLP-1/GIP/glucagon agonist that is being developed for the treatment of obesity. In this study, we investigated whether treatment with HM15211 prevents bone loss under a severe weight loss condition, and the underlying mechanism of action. First, the bone protective effect of HM15211 was evaluated using diet induced obesity ovariectomized osteoporosis rat model. After 4 weeks subcutaneous treatment of HM15211 (120 µg/kg xG3QO), lower levels of serum deacylslated osteocalcin (42.2 ng/mL) and higher serum PINP (procollagen type I pro-peptide, 53.2 ng/mL) were observed compared with those of vehicle (156.4 ng/mL for osteocalcin, 28.6 ng/mL for PINP) and liraglutide-treated groups (94 µg/kg xBID, 120.6 ng/mL for osteocalcin, 29.4 ng/mL for PINP). Furthermore, HM15211 showed comparable BMD of femur bones and lumbar spine with vehicle group while weight loss was greater (-26.0% vs. vehicle). These results suggest that treatment with HM15211 prevents bone loss even after potent body weight loss in high fat dieted ovariectomized obese rats. Second, to elucidate the underlying molecular mechanism, related marker gene expression was investigated using the SaOs2 cell, human osteogenic cell. In line with the bone protective effect in vivo, HM15211 led to significant increases in type I collagen-α1, -α2, and carboxylated osteocalcin expression, which were blunted by inhibition of GIPR-mediated signaling.

In conclusion, these results suggest that HM15211 might provide potent weight loss without the otherwise inevitable bone loss.

Effect of a Novel Long-Acting GLP-1/GIP/Glucagon Triple Agonist (HM15211) in a NASH and Fibrosis Animal Model

IN YOUNG CHOI, JUNG KUK KIM, JONG SUK LEE, EUJIN PARK, YOUNG HOON KIM, SUNG YOUB JUNG, SUN JIN KIM, Seoul, Republic of Korea

Nonalcoholic steatohepatitis (NASH), a potential consequence of NAFLD, may lead to end stage liver diseases including cirrhosis and hepatocellular carcinoma. Despite its severity and prevalence, NASH currently lacks effective treatment. In this respect, we developed a novel long-acting, GLP-1/GIP/glucagon triple agonist, HM15211. With a unique activity profile, HM15211 could provide synergetic benefits on body weight loss and lipid profile improvement while avoiding hyperglycemic risk. Previously, we showed that HM15211 exerts potent reductions in body weight and hepatic TG (triglycerides) in DID mice, and showed a liver preferential distribution, suggesting HM15211 as a potential treatment for NASH. Here, we evaluated the effect of HM15211 in NASH and fibrosis using MCD-diet mice with various disease induction periods. In MCD-diet mice (6 weeks induction), HM15211 treatment led to significant decrease in hepatic TG (-82.6% vs. vehicle) and TBARS (oxidative stress marker, -60.7% vs. vehicle), which coincided with significant reduction in ALT and bilirubin. Time course MRI/MRS imaging further confirmed the progressive steatosis resolution by HM15211. Furthermore, histopathological analysis indicated that HM15211 significantly reduced hepatocellular inflammatory gene expression and NAFLD activity score (1.3 for HM15211, 3.4 for liraglutide, and 2.7 for vehicle). To further evaluate the therapeutic potential in fibrosis, MCD-diet mice was used for the disease induction period (10 weeks induction) to achieve overt liver fibrosis. In line with NASH improvement, HM15211 successfully resolved liver fibrosis as demonstrated in histological evaluation. Histological improvements were accompanied by a remarkable decrease in disease biomarkers including hepatic hydroxyproline. Based on these observations, HM15211 may offer a therapeutic potential for NASP and fibrosis as well as obesity.

1107-P
Neuroprotective Effects of HM15211, a Novel Long-Acting GLP-1/GIP/Glucagon Tripeptide Agonist in the Neurodegenerative Disease Models

JEONG A. KIM, SANGDON LEE, SANG HYUN LEE, SUNG YOUB JUNG, YOUNG HOON KIM, IN YOUNG CHOI, SUN JIN KIM, Seoul, Republic of Korea

HM15211 is a novel long-acting GLP-1/GIP/glucagon tripeptide agonist that is being developed for the treatment of obesity and nonalcoholic fatty liver disease (NASH). Accumulating evidences have shown that obesity, type 2 diabetes, and NASH increase the risk of developing progressive neurodegenerative disease such as Parkinson’s disease (PD) and Alzheimer’s disease (AD). In addition to peripheral contributions, each of incretins consisting HM15211 have neuroprotective effects in several brain diseases like AD, PD, and ischemia. Previously, we demonstrated that HM15211 exerted neuroprotective effects in MPTP-induced PD model. Here, we evaluated 1 ) the neuroprotective effects of HM15211 in chronic MPTP/probenecid PD model, and 2) the protection of AD progression in db/db mice. Chronic PD model was induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in combination with probenecid injection, twice a week for 5 weeks and HM15211 was administered once a week for 6 weeks. Dopaminergic neuronal death by MPTP/probenecid was protected by HM15211, which was derived from anti-inflammatory and anti-oxidative stress effect by HM15211. Also HM15211 decreased alpha synuclein in striatum of chronic mouse PD model. Together with these efficacies, HM15211 significantly improved the MPTP/probenecid induced motor impairments in behavior. A db/db mouse are well-established diabetic model and reported that db/db mouse develop hyperphosphorylation of tau as they grew older. Thus we chose db/db mice to elucidate the prophylactic effect of HM15211 on AD. After once every 2 days subcutaneous administration for 12 weeks, HM15211, reversed inflammatory cytokines and oxidative stress marker, which were increased in db/ db mice. Also, increased phosphorylated tau in db/db mice was decreased by HM15211. Based on these observations, HM15211 might be a potential therapeutic option for the neurodegenerative disease.

1108-P
Efficacy and Safety of Glucagon-Like Peptide-1 Receptor Agonist (GLP-1RA) plus Basal Insulin vs. GLP-1RA in Type 2 Diabetes Mellitus—A Systematic Review and Meta-analysis

MUNEEZA M. SATTLI, TIMOTHY D. BRIEN, AARON LIEW, Galway, Ireland

Combination therapy with Glucagon-like peptide-1 receptor agonist (GLP-1RA) and basal insulin represents a new therapeutic option for diabetes mellitus. We hypothesized that GLP-1RA plus basal insulin is more efficacious, safer and tolerable than GLP-1RA for patients with type 2 diabetes mellitus.
Possibility of Liraglutide for Prevention of Dementia Progression in Patients with Type 2 Diabetes

MAIMI YOSHIDA, TAKAKO MORIMOTO, ERIKO OH, NAOMUNE YAMAMOTO, KOUJI NAGATA, AKIO SAKI, EUN SASKI, SHIGERU YOSHIDA, TAKESHI KUZUYA, NAKAAI OHSAWA, MASAKAZU SUGINO, Ishibashi Japan Osaka Japan

Purpose: The aim of this study was to assess the efficacy of liraglutide on prevention of dementia in elderly patients with type 2 diabetes (T2DM).

Subjects and methods: We studied 34 (male 8/female 26) outpatients with 65 years or older, whose HbA1c was over 7.0% by other antidiabetic treatment. We administrated liraglutide 0.3mg before breakfast for the first week, 0.8mg for the second week, and 0.9mg after the third week. Patients in the liraglutide group (G group) (8 males/26 females, 75.7±7.8 years old, HbA1c 7.5±0.38%) were followed-up for 3 years. We examined voxel-based Specific Regional Analysis System for Alzheimer’s Disease (VSRAD) on MRI, max-IMT measured by carotid artery echo, visceral fat area, HbA1c, FPG, serum HDL/DL level, and TG, both before and after the treatment.10 patients in the liraglutin group (D group) in which age, HbA1c, visceral fat, and VSRAD were matched with G group were used as controls.

Result: After 3 years, VSRAD was not changed in G group and was significantly deteriorated in D group (G group: 1.22±0.73 vs. D group: 2.08±1.72 (p<0.05)). Max-IMT was significantly improved in G group (2.42±1.65→2.14±1.04 (p<0.05)) vs. 2.25±1.19→2.19±1.01 (NS)). Visceral fat was significantly reduced in G group (131.4±59.3→123.0±59.3 (p<0.01) vs. 114.3±55.8→116.5±66.2 (NS)). HbA1c (17.5±3.8→8.6±1.4 (p<0.01) vs. 7.3±0.55→6.9±0.42%), FPG (137±19→121±11 vs. 135±21→118±16 mg/dl), were significantly improved in both groups (p<0.01). No hypoglycemia requiring medical intervention was observed. Lipid was significantly improved only in G group. There was no onset of dementia.

Conclusion: Liraglutide improved the glycemic control, lipid profile, and visceral obesity of elderly patients with T2DM for 3 years. In addition, the hippocampal atrophy and atrophia were not deteriorated, suggesting the possibility of being effective for prevention of dementia.
Heterologous Adipose-Derived Mesenchymal Stem Cells and Vitamin D Supplementation in Patients with Recent-Onset Type 1 Diabetes Mellitus—Six Months Follow-Up

JOANA R. GANTAS, DEBORA A. CABRAL, SR., KARINA PEREIRA, MARIA F. PEREIRA, DEBORA L. SOUTO, MATHEUS NOLASCO, MARINA D. SOARES, MONICA GABBAY, CARLOS E. COURI, CESAR S. CLAUDIO-DA-SILVA, CARMEN K. REBELATTO, SERGIO A. DIIB, JOSE EDGIO P. OLIVEIRA, LENITA ZAJDENVERG, MELANIE RODACKI, Spring House, PA, Rantan, NJ

Objective: To evaluate the safety and efficacy of 6 months follow-up of infusion of heterologous adipose tissue derived mesenchymal stem cells (ADMSCs) of healthy donors + daily cholecalciferol (VD) in patients with recent-onset T1D.

Methods: In this prospective open trial, patients with recent-onset T1D between 18-35 y/o received a single infusion of heterologous ADMSCs (kg x 10^6) + daily oral VD (2000UI). Glycated hemoglobin (HbA1c), basal and stimulated C-peptide (CP) after a mixed meal, insulin dose, adverse events, and glycemic variability (GV) through continuous glucose monitoring (CGM) were assessed at baseline (T0), after 3 (T3) and 6 (T6) months. Patients were compared to controls with recent-onset T1D included in previous study that received 1) standard insulin treatment (INS); 2) insulin and VD. Chi-square and Wilcoxon tests were used for statistical analysis.

Results: Six patients (3 males) with mean age of 27 ± 7.1 y/o underwent ADMSC + VD intervention. There were no differences in insulin dose/kg (p=0.6), peak CP (p=0.075) and area under the stimulated CP curve (p=0.25). All patients had increase in basal CP (p=0.03). HbA1c improved at T3 (0.03), with no difference at T6 (p=0.07). GV did not change after intervention. Increase in Basal CP and stimulated CP were similar between groups, ADMSCs+VD, VD and INS (basal CP=100% vs. 58.8% vs. 45%, respectively, p=0.057, and stimulated CP=66.7% vs. 58.8% vs. 25% p=0.058). One patient developed central retinal vein occlusion at T3, with resolution at T6 and another had recurrence of a benign ovarian tumor at T6.

Discussion: In patients with T1D, heterologous ADMSCs + VD supplementation is feasible and appears to be safe after 6 months of follow-up and resulted in improvement of basal CP. Although GV did not change after the infusion, all patients had an excellent glycemic control, preserved β-cell function and low insulin requirements after the intervention with little complications.

Supported By: Hannmi Pharm. Co., Ltd, Sanofi

Cholesterol 7 Alpha-Hydroxylase (CYP7A1) Activity and 7-Alcoholysis—Are Not Translatable Biomarkers of Glucagon Receptor (GCGR) Activation

RAUL CAMACHO, WENYING JIAN, BIN GAO, WENYING JIAN, BING DING, FANY BONILLA, THOMAS KIRCHNER, RUI ZHANG, ANNE M. RENTZ, SURESNES, FRANCE, Boston, MA

Glucagon-like peptide 1 receptor/glucagon receptor (GLP-1R/GCGR) dual agonists are being pursued for obesity and type 2 diabetes mellitus (T2DM). A biomarker for GCGR would aid in optimizing receptor balance and in modeling dose selection to avoid potential adverse events from excess GCGR agonism. It has been reported that glucagon treatment decreases CYP7A1 transcription in primary rat and human hepatocytes, whereas GCGR antagonists increase CYP7A1 mRNA in mice and its product, 7-HCO (the precursor of C4), in diabetic patients. We tested glucagon, insulin, darglutide, and a GLP-1R/GCGR dual agonist, Cpd. A, in primary human and cynomolgus monkey hepatocytes. All treatments decreased CYP7A1 expression in monkey hepatocytes. C4 was undetectable in the culture media. Lean mice or rats treated with Cpd. A showed no changes in non-fasting C4. Diet-induced obese mice treated with Cpd. A or a GCGR-null analog had decreased non-fasting C4. To test whether GCGR (and/or GLP-1R) agonism affects plasma C4 in higher species, we infused saline or glucagon (at two different rates) on a background of somatostatin infusion in cynomolgus monkeys dosed with darglutide the day before. C4 levels did not differ between treatment groups. To determine whether this lack of an effect was specific to pre-clinical studies, T2DM patients were dosed once a week for 4 weeks with a placebo or 2 doses of a second GLP-1R/GCGR dual agonist. There were no statistically significant differences in C4 levels between groups. Hence, in contrast to GCGR antagonists, GCGR and/or GLP-1R agonists did not modulate C4 levels in pre-clinical species or in T2DM patients.

Cost-utility analyses include health utilities to compare medical treatments. Health utilities, ranging from 0 to 1, represent the strength of a patient’s preference for a drug profile or health-related outcome. Recently glucagon-like peptide-1 (GLP-1) receptor agonists have been used for management of glycemic control in type 2 diabetes (T2DM). Many GLP-1 drugs have similar modes of administration. In contrast, ITCA 650 is an investigational product which is an implantable device that, following subdermal placement, provides continuous delivery of exenatide for 3 or 6 months. The study’s purpose was to estimate health utilities associated with treatment processes of GLP-1s for use in economic models. During a UK-based pilot study, 19 general population (general population) participants completed time trade-off (TTO) interviews to value health states (often called vignettes or scenarios) which were based on literature review, instructions for use, and clinician interviews. A follow-up pilot study was conducted in both general population and T2DM participants to value modified health states. Participants were recruited to ensure equal distribution across gender and education levels. A total of 20 general population and 18 T2DM patients completed face-to-face interviews (general population mean age = 50.7, T2DM mean age = 56.2). Mean utilities (SD) for ITCA-650 were 0.93 (0.06) for T2DM patients and 0.91 (0.11) for the general population. Mean utility scores for injection health states ranged from 0.83 (0.92) for T2DM and 0.82-0.91 for general population. Results are higher than others found in the literature for diabetes treatment processes (range: 0.85 to 0.88). A main study with 200 participants will be conducted in early 2018. Results may be useful in cost-utility models comparing the value of treatment processes for patients with T2DM. Findings suggest the TTO method may be used to quantify preferences among different treatment processes.

Supported By: Servier; Intarcia Therapeutics, Inc.
**1115-P**

**IMG-1 Is Able to Normalize Blood Glucose Levels by Inhibiting Glucagon Levels in a Type 2 Diabetic Rat Model**

JONATHAN B. POLLETT, NGOC THAI, Devon, PA

IMG-1 is a novel therapeutic compound for the treatment of diabetes. Ten-week-old diabetic ZDF rats were treated with IMG-1 either intravenously (IV) or per oral (PO) once a day and compared to no treatment over a thirty-five-day period. Weights and glucose levels were monitored twice a week. IMG-1 treated animals showed a marked decrease in BG levels within a week, laverage BG levels of 179mg/dl for IMG-1 (IV) and 153mg/dl for PO. This finding was enduring for the entire 35-day period. Untreated controls had significantly elevated BG levels throughout the study, with average levels exceeding 400mg/dl (481mg/dl). Hemoglobin Alc (HbA1c) was measured at days 0 and 35. IMG-1 treated animals had significantly lower HbA1c (IV, 9.7%± 7.4%) and PO (10.8% -7.5%) while the untreated group maintained increased HbA1c levels (10.2% -12.3%). There was no significant difference in insulin levels between untreated and IMG-1 treated groups at any time point suggesting IMG-1 decreased insulin resistance. Glucagon levels were reduced in both IV and PO (IMG-1 treated animals at days 15 from (115pg/ml and 119pg/ml) to 90pg/ml and 92pg/ml, respectively) and 35 (89pg/ml and 92pg/ml). Control animals had no significant difference in glucagon levels throughout the entire study. Based on these results, it appears that IMG-1 is able to normalize both blood sugar in ZDF animals and lower HbA1c and decrease glucagon levels without elevating insulin levels in these animals.

**CLINICAL THERAPEUTICS/NEW TECHNOLOGY—ORAL AGENTS**

**Moderated Poster Discussion: New Concepts in Oral Therapies (Posters 1116-P to 1121-P); see page 17.**

**1116-P**

**Dapagliflozin Suppresses Plasma Pepcidin Concentrations**

HUSAM GHANIM, JEANNE M. HEJNA, SANAA ABUJARHEH, TANVI SHAH, JAGDESH KUMAR, MANAV BATRA, PARESH DIANDONA, Buffalo, NY, Williamsville, NY

Dapagliflozin and other SGLT2 inhibitors are known to increase hematocrit. One possible mechanism is glycosuria and polyuria and the loss of fluid from the vascular compartment. However, since type 2 diabetes is a pro-inflammatory state and since hepcidin, a known suppressor of erythropoiesis, is increased in pro-inflammatory states, we investigated the possibility that dapagliflozin suppresses hepcidin concentrations and thus increases erythropoiesis. Twenty-two patients with type 2 diabetes and normal renal function (mean age: 62±1.7 years) were randomly treated with placebo or dapagliflozin 10 mg daily for 12 weeks. In the dapagliflozin group, there was a fall in HbA1c from 7.1±0.2% to 6.7±0.2% (p<0.05), increase in hemoglobin concentration from 13.2±0.7g/L to 13.8±0.4g/L (p<0.05) and in Hct from 40.2±1.3% to 41.9±1.8% (p<0.05). Plasma concentration of hepcidin fell from 265±26ng/mL to 215±24ng/mL (p<0.05). There was no significant change in any of these indices in the placebo group. Since one of the mechanisms through which hepcidin inhibits erythropoiesis is the suppression of the expression of ferritin, which transports iron from iron storage cells into plasma, we also measured ferritin expression in peripheral blood mononuclear cells. The expression of this transporter was not altered. We conclude that dapagliflozin suppresses hepcidin concentrations significantly, consistent with an increase in erythropoiesis and hematocrit but by a mechanism not involving ferritin expression.

Supported By: AstraZeneca

**1117-P**

**An Allosteric Glucagon Receptor Antagonist, LGD-6972, Displays Biased Receptor Signaling**

ERIC G. VAJDA, LIN ZHI, KEITH MARSHCKE, San Diego, CA

Glucagon receptor antagonists (GRA) are novel molecules in development for the treatment of type 1 and type 2 (T2DM) diabetes. LGD-6972 recently demonstrated robust efficacy in a 12-week, Phase 2 study in T2DM, reducing HbA1c by 1.2% from baseline, with a safety profile more favorable than other GRAs at this stage of development. LGD-6972 is structurally distinct from other small molecule GRAs, containing a sulfonic acid tail (SAT), potentially explaining this finding. We performed computational modeling of LGD-6972 bound to the glucagon receptor (GCGR) and compared it to x-ray crystallography data with receptor- ligand complexes of exenatide. No critical finding was observed in the subchronic toxicity studies. In vitro, LGD-6972 displays receptor-biased signaling. To further investigate the potential differences among compounds, primary human hepatocytes were treated with glucagon or glucagon or LGD-6972 and gene expression was analyzed by microarray. Broad differences between glucagon and the GRAs were observed and future studies will investigate the effects of SAT and CAT compounds.

**1118-P**

**OWL833, an Orally Active Nonpeptide GLP-1 Receptor Agonist, Improves Glucose Tolerance by Increasing Insulin Secretion and Reduces Food Intake of Cynomolgus Monkeys**

TAKAHIRO KAWAI, FUMIHITO TANINO, MASANORI FUKAZAWA, KOTARO OGAWA, SHUNSUKE NAGAO, HITOSHI YOSHINO, SHUN-ICHIRO KOMATSU, YOSHIYUKI SUZUKI, YOSHIKI KAWABE, Gotemba, Japan, Hyogo, Japan, Kamakura, Japan, Shizuoka, Japan

Activation of glucagon-like peptide-1 receptors (GLP-1R) is a promising approach for the treatment of type 2 diabetes mellitus (T2D), and several peptide analogues of GLP-1 have been successfully developed. Here we identified a new orally active non-peptide GLP-1R agonist, OWL833, and examined its efficacy in cynomolgus monkeys. The agonistic activity of OWL833 was evaluated by measuring cAMP accumulation in cells expressing mammal GLP-1Rs and other glucagon family receptors. In the cells expressing human or cynomolgus monkey GLP-1R, OWL833 (1μM) produced a 1.2-fold cAMP accumulation to the same level achieved by GLP-1, and its EC50 values for human and cynomolgus monkey GLP-1Rs were the same at 1.1 nmol/L. In contrast, OWL833 showed no stimulatory activity on human glucagon, GIP, and GLP-2 receptors. The predicted bioavailability and T1/2 of OWL833 in human based on rodent and non-rodent experimental data are 30% and ~18 hour, respectively. After OWL833 followed by glucose was intravenously injected in cynomolgus monkeys, OWL833 decreased the blood glucose level via insulin secretion to the same extent as effective concentrations of exenatide, a GLP-1 peptide mimetic, in clinic. Doses of 0.05 and 0.1 mg/kg OWL833 given orally to cynomolgus monkeys reduced their food intake by 25% and 45%, respectively, as compared with vehicle group, and the effect on food intake was equal to that of 0.3 and 0.6 μg/kg subcutaneous injections of exenatide. No critical finding was observed in the chronic toxicity studies in rats and cynomolgus monkeys. These findings demonstrate that OWL833 has full agonistic activity on human and cynomolgus GLP-1R and improves glucose tolerance by stimulating insulin secretion, and that it exhibits an anti-feeding activity similar to exenatide. In conclusion, OWL833 has potential as a once-daily, orally active, non-peptide GLP-1 receptor agonist.

**Alteration of Gut Microbiota Induced by DPP-4i Treatment Improves Glucose Homeostasis**

XIAOYU LIANG, HONGTING ZHENG, Chongqing, China

Background and Aims: Emerging evidence indicates that the gut microbiota contributes to the occurrence and development of metabolic diseases. While, little is known about the effect of dipeptidyl peptidase-4 inhibitors on the gut microbiota. In the current study, we investigated the role of DPP-4i and acarbose in modulating the gut microbial community.

Methods: 16S rRNA sequencing was performed to analyze the effect of DPP-4i and acarbose on the gut microbiota in HFD mice. Fecal microbiota transplantation (FMT) from DPP-4i, acarbose, or placebo- treated T2D patients to germ-free (GF) mice was performed to investigate the contribution of the altered microbiota to the anti-diabetic effect. Fecal metabolomics were analyzed by targeted and untargeted GC-MS system.

Results: DPP-4i and acarbose changed the gut microbiota composition, and the DPP-4i- altered microbiota improved the glucose tolerance, while acarbose- altered microbiome did not. Moreover, DPP-4i primarily reduced the burden MK-0983. The SAT of LGD-6972 creates a larger pocket between helix 6 and 7 in the GCGR transmembrane domain, and alters the orientation of helix B. Activity of LGD-6972, MK-0883 and other SAT and CAT GRAs were examined in cellular models of glucagon-stimulated cAMP accumulation, β-arrestin recruitment, and receptor internalization. All tested GRAs were full (≥95%) antagonists of cAMP accumulation. CAT GRAs were full antagonists of β-arrestin (≥96%) and receptor internalization (≥94%). In contrast, SAT GRAs had reduced antagonism of β-arrestin (58-87%) and receptor internalization (6-52%). The relative potency was also altered with greater potency for CAT GRAs vs. CAMP, whereas the opposite was true for SAT GRAs. Furthermore, a LGD-6972 analog with a CAT and a MK-0883 analog with a SAT displayed CAMP- and SAT-like activity, respectively, indicating a clear structure-activity relationship exists, with LGD-6972 displaying receptor-biased signaling. To further investigate the potential differences among compounds, primary human hepatocytes were treated with glucagon or glucagon or LGD-6972 and gene expression was analyzed by microarray. Broad differences between glucagon and the GRAs were observed and future studies will investigate the effects of SAT and CAT compounds.

**1119-P**

**Moderated Poster Discussion**

**ADA-Supported Research**
ratio of Firmicutes to Bacteroidetes, and changed the pattern of metabolites in HFD mice, especially the increase of succinate.

Conclusions: Our findings demonstrated that the alterations of the gut microbial composition and metabolites might be previously unsuspected hypoglycemic mechanism of DPP-4I. It might provide a potential strategy for modulating glucose homeostasis in the future.

Figure.

**Pioglitazone Alters the Cargo Composition of Circulating Exosomes in Subjects with Type 2 Diabetes**

YURY O. NUNEZ LOPEZ, RICHARD E. PRATLEY, Orlando FL

Pioglitazone (PIO) is an agonist of peroxisome proliferator-activated receptor-γ (PPARγ) which is predominantly expressed in adipose tissue and improves insulin sensitivity in patients with type 2 diabetes (T2D). We hypothesized that PIO effects are mediated, at least in part, by changes in the cargo composition (specifically, miRNAs) of circulating exosomes. We tested this hypothesis in a 3-month trial in which 24 patients with T2D who were well-controlled (HbA1c ≤ 7.0%) with diet/exercise or metformin were randomized to either PIO or placebo (PLA) treatment (NCT00656864).

Levels of 42 miRNAs expressed in adipocyte exosomes were measured in exosomes isolated from fasting plasma samples obtained before and after treatment. Levels of exosomal miR-374b-5p, miR-20a-5p, miR-7-5p, and miR-195-5p changed significantly (fold change > 1.5, P < 0.05, FDR < 0.17) in response to PIO treatment relative to PLA (Figure). Changes in exosomal miRNAs correlated with changes in fasting glucose and insulin levels (r > 0.4, P < 0.05, FDR < 0.1). These data suggest that the change in the abundance of specific miRNAs in circulating exosomes may serve as a biomarker of response to PIO and that exosomal miR-374b-5p, miR-20a-5p, miR-7-5p, and miR-195-5p might play mechanistic roles in long-range inter-organ crosstalk.

**FTY720 Treatment Rejuvenates β-Cell Function and Improves Cardiovascular Outcomes in Diabetic Nonhuman Primates (NHPs)**

YIXIN WANG, YONGJIAO LIU, QIAO WEI, XIAOLI WANG, GAO SUN, YONG-FU XIAO, GUILIANG YU, ZHONGMIN A. MA, Taichang China, Suzhou, China, Great Neck, NY

Pancreatic β-cell regeneration is considered as a possible therapy for cure of type 2 diabetes (T2D). It has been reported that administration of FTY720, a sphinogosine 1-phosphate (S1P) receptor modulator, to db/db mice led to sustained normalization of hyperglycemia by stimulating β-cell in vivo regeneration through PDK-dependent regulation of cyclin D3 and p53[ref]. To further evaluate the therapeutic potential of FTY720 in the treatment of T2D, we examined the effects of FTY720 on glucose homeostasis in an established diabetic NHP model. NHPs with mean fasting glucose (FG) level of 249 mg/dL were randomly divided into the control (vehicle) and the FTY720-treatment group. FTY720 was orally administered at 5 mg/kg to diabetic NHPs once per day and the FG and HbA1c levels were measured biweekly. Here we show that FTY720 treatment of diabetic NHPs significantly lowered their FG and HbA1c in two weeks. After 10 weeks of treatment, their FG and HbA1c levels remained low and their glucose tolerance was significantly improved. To determine the effect of FTY720 on β-cell function, IVGTT was performed. Following glucose injection, the insulin levels in the control NHPs barely changed. In contrast, the FTY720-treated NHPs secreted large amount of insulin in response to glucose stimulation, consistent with β-cell in vivo regeneration observed in mice. We also evaluated the cardiac function in these NHPs by echocardiography, from which ejection fraction (EF) and fractional shortening (FS) are found abnormally low in diabetic NHPs (EF=60% and FS=30%) than that in normal NHPs (EF=68% and FS=43%). After 10 weeks of treatment, however, EF in the treatment group was significantly increased from 60% to 70% and FS from 30% to 38% while these values remained abnormally low in the control group. Our data strongly suggest that FTY720 has a great therapeutic promise for the treatment of T2D with benefit to improve the cardiac function in the patients.

**Sotagliflozin (SOTA) is a Dual SGLT1 and SGLT2 Inhibitor, as Adjunct Therapy to Insulin in Adults with Type 1 Diabetes (The European inTandem2 Study)**

THOMAS DANNE, BERTRAND CARIOU, PHILLIP L. BANKS, MICHAEL BRANDLE, HELMUT BRATH, EDWARD FRANEK, JAKE A. KUSHERN, PABLO LAPUERTA, DARREN K. MCGUIRE, ANNE L. PETERS, SANGEETA SAWHNEY, PAUL STRUMPH, Hannover, Germany, Nantes, France, The Woodlands, TX, Kantonsspital St. Gallen, Switzerland, Vienna, Austria, Warsaw, Poland, Houston, TX, Basking Ridge, NJ, Dal-la-, TX, Los Angeles, CA

Supported By: Florida Hospital

Sotagliflozin (SOTA) is a dual SGLT1 and SGLT2 inhibitor in development as adjunct therapy to insulin in T1D.

In this double-blind, 52-week study, 782 adults with T1D treated with multiple daily insulin injections or pump therapy were randomized 1:1:1 to placebo (n=258), SOTA 200 mg (n=261) or SOTA 400 mg (n=263) once daily after 6 weeks of insulin optimization. Primary endpoint was change from baseline in A1C at Week 24. Other endpoints included A1C, documented hypoglycemia (DH), weight and FPG change at Week 52, patient (pt) reported outcomes (PROs) and net clinical benefit (NCB), assessing the proportion of pts with A1C <7.0% without severe hypoglycemia (SH) or diabetic ketoacidosis (DKA).

Baseline characteristics were similar between groups. Compared with placebo, treatment with SOTA 200 or 400 mg improved A1C and pt satisfaction at Week 24 and reduced A1C, DH rate, weight, FPG and pt distress at Week 52 (Table). More pts achieved NCB in the SOTA arms vs. placebo (Table). Pts receiving SOTA 400 mg had the least SH events, but more genital mycotic infections, IKA and diarhoea than placebo.

**Clinical Diabetes/Therapeutics POSTERS**

Moderated Poster Discussion: Clinical Outcomes with Oral Therapies
(Posters: 1122-P to 1127-P), see page 19.
In conclusion, SOTA 200 and 400 mg were associated with statistically significant A1C reductions that were sustained (P<0.05) at Week 52, as well as improved DH and PROs. There was more DKA, but less SH, with SOTA 400 mg relative to placebo at Week 52.

**Table. Efficacy (mITT Population) and Safety (Safety Population) Results.**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo n=258</th>
<th>SOTA 200 mg n=251</th>
<th>SOTA 400 mg n=239</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean A1C at Baseline after 6-week insulin optimization, %</td>
<td>7.79</td>
<td>7.54</td>
<td>7.71</td>
</tr>
<tr>
<td><strong>Outcomes at Week 24</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1C LSM difference from placebo, % ± SE (P-value)</td>
<td>-0.37±0.06 (P=0.001)</td>
<td>-0.35±0.06 (P=0.001)</td>
<td></td>
</tr>
<tr>
<td>FPG LSM difference from placebo, mmol/L ± SE (P-value)</td>
<td>-0.2±0.03 (P=0.001)</td>
<td>-0.3±0.03 (P=0.001)</td>
<td></td>
</tr>
<tr>
<td>Daily insulin LSM difference from placebo, IU ± SE (P-value)</td>
<td>-2.81±1.14 (P=0.014)</td>
<td>-3.37±1.14 (P=0.003)</td>
<td></td>
</tr>
<tr>
<td>DHR ratea, LSM difference from placebo ± SE (P-value)</td>
<td>-0.03±0.01 (P=0.17)</td>
<td>-0.03±0.01 (P=0.056)</td>
<td></td>
</tr>
<tr>
<td>Body weight LSM difference from placebo, kg ± SE (P-value)</td>
<td>-2.1±0.36 (P=0.001)</td>
<td>-2.7±0.36 (P&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Mean daily bolus insulin dose at Baseline, IU</td>
<td>32.1</td>
<td>31.1</td>
<td>31.9</td>
</tr>
<tr>
<td>Bolus insulin dose mean change from Baseline, % ± SE</td>
<td>4.2±1.25</td>
<td>-3.48±3.24</td>
<td>-7.94±2.23</td>
</tr>
<tr>
<td>Bolus insulin LSM difference from placebo, % ± SE (P-value)</td>
<td>-7.70±4.41 (P=0.038)</td>
<td>-12.15±4.40 (P=0.050)</td>
<td></td>
</tr>
<tr>
<td><strong>Net clinical benefit at Week 52</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1C &lt;7.0% without SH and without DKA, n (%)</td>
<td>37 (14.3)</td>
<td>67 (26.2)</td>
<td>70 (26.6)</td>
</tr>
<tr>
<td><strong>Safety outcomes over 52 weeks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any TEAE, n (%)</td>
<td>158 (61.2)</td>
<td>178 (68.2)</td>
<td>181 (68.8)</td>
</tr>
<tr>
<td>TEAEs leading to study discontinuation, n (%)</td>
<td>9 (5.5)</td>
<td>10 (5.8)</td>
<td>8 (3.8)</td>
</tr>
<tr>
<td>Treatment-emergent serious adverse events, n (%)</td>
<td>17 (6.5)</td>
<td>26 (10.0)</td>
<td>21 (8.0)</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>2 (0.8)*</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DKA, n (%)</td>
<td>0</td>
<td>6 (2.3)</td>
<td>9 (3.4)</td>
</tr>
<tr>
<td>Severe hypoglycemia, n (%)</td>
<td>13 (5.0)</td>
<td>13 (5.0)</td>
<td>6 (2.3)</td>
</tr>
<tr>
<td>Diamine, n (%)</td>
<td>9 (3.5)</td>
<td>12 (4.8)</td>
<td>19 (7.2)</td>
</tr>
<tr>
<td><strong>Patient reported outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTSQ score, A1C LSM difference from placebo at Week 24 ± SE (P-value)</td>
<td>2.0±0.4 (P=0.001)</td>
<td>1.7±0.4 (P&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>DDS2 score, A1C LSM difference from placebo at Week 52 ± SE (P-value)</td>
<td>-0.2±0.2 (P=0.046)</td>
<td>-0.3±0.2 (P=0.001)</td>
<td></td>
</tr>
</tbody>
</table>
| DDS2, two-item Diabetes Distress Screening Scale (negative scores indicate improvement); DH, documented hypoglycemia; DKA, diabetic ketoacidosis; DTSQ, diabetes treatment satisfaction questionnaire; FPG, fasting plasma glucose; LSM, least squares mean; mITT, modified intent-to-treat; SE, standard error; SH, severe hypoglycemia; SOTA, sotagliflozin; TEAE, treatment emergent adverse events. *One death was due to cardiopulmonary failure and the other to a malignant lung neoplasm. †Events per patient per day <3.0 mmol/L (<65 mg/dL). ‡Positively-adjudicated events (defined as an adjudicator assessment of yes/certainly or yes/probably), discontinuation of drug due to DKA was: 0% placebo, 0% SOTA 200 mg, and 1.9% for SOTA 400 mg; ‡Discontinuation of drug due to diarrhea was: 0.4% placebo, 0.8% SOTA 200 mg, and 0.8% SOTA 400 mg.}

Cumulative Delays in Treatment Intensification over Three Typical Stages of Antihyperglycemic Treatment

SUMA VUPPUTURI, Rockville, MD

Although delays in treatment intensification (TI) have been documented for anti-hyperglycemic medications, cumulative delays over the life course of diabetes treatment have not been reported. We combined 2005-2016 data from the Northwest and Mid-Atlantic regions of Kaiser Permanente to identify 248 patients who: (1) initiated metformin (MET); (2) then added a sulfonylurea (SU) to existing MET; and (3) initiated insulin (INS) after MET or SU. We used the date of the initiation of each stage of therapy to calculate time between A1C ≥2% and TI, pre-TI A1C, post-TI A1C, and achievement of A1C goal ≥7% within one year of TI. We also measured time to intensification within 6 months prior to TI. Mean or median cumulative measures were summed across the three TI stages. Among patients who experienced each stage of MET, SU, and INS intensification, the mean A1C percentage points outside of goal summed to 5.9 (Table). These patients accrued a median of 191 days of TI delays in the 3-6-month periods preceding TI. Although A1C was lowered after each stage of TI, a minority of patients achieved A1C goals of ≤7% resulting in accumulation of a mean of 3.3 excess A1C percentage points over the 3 one year periods after TI of MET, SU, and INS. TI delays occur at every stage of diabetes therapy. Glycemic burden accumulates over the life course of diabetes and may result in differential complication risks. However, further study is needed.

Empagliflozin (EMPA) Reduces Mortality and Hospitalization for Heart Failure (HHF) Irrespective of Cardiovascular (CV) Risk Score at Baseline

DAVID H. FITCHETT, BENJAMIN M. SCRICA, SILVIO INZUCCHI, CHRISTOPHER P. CANNON, DARREN K. MCGUIRE, COO ERIK JOHANSEN, STEVEN SAMBEVSKI, UWE HENIKE, JOTHIS T. GEORGE, BERNARD DRUZAN, TORONTO, ON, Canada; Boston, MA; New Haven, CT; Dallas, TX; Asker, Norway; Ingelheim, Germany

In the EMPA-REG OUTCOME trial, EMPA added to standard of care reduced CV death vs. placebo (PBD) by 38% (HR 0.62 [95% CI 0.49, 0.77]), all-cause death by 32% (HR 0.68 [95% CI 0.57, 0.82]) and HHF by 25% (HR 0.75 [95% CI 0.63, 0.90]) in patients with type 2 diabetes and established CV disease. We investigated CV death, all-cause death, HHF and the composite of HHF or CV death by degree of baseline CV risk using the 10-point TIMI Risk Score for Secondary Prevention (TRS 2°P). P-values for treatment-by-subgroup interaction were obtained from tests of homogeneity of treatment group differences among subgroups with no adjustment for multiple testing.

Based on the TRS 2°P risk score, of 7020 patients who received study drug in the EMPA-REG OUTCOME trial, 12%, 40%, 30% and 18% were at low, intermediate, high and highest residual CV risk, respectively, at baseline. In the placebo group, from low to highest predicted risk, the proportion of patients with CV death increased from 2.2% to 11.2% and the proportion of patients with HHF increased from 1.1% to 10.0%. Effects of EMPA on CV death, all-cause death, HHF and HHF or CV death were consistent across subgroups by baseline CV risk score (Figure).

In conclusion, the benefits of EMPA on key clinical outcomes in the EMPA-REG OUTCOME trial occurred irrespective of the degree of baseline CV risk.

The issue of TIMI 2°P risk score and outcomes has been previously published. FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HR, hazard ratio; LVH, left ventricular hypertrophy; TIMI, Thrombolysis in Myocardial Infarction; SU, sulfonylurea; TIMI 2°P, Treatment-by-Intention-to-Treat 2°P Risk Score; Tl, time to; TRS 2°P, Treatment-by-Risk Score 2°P; W, week. *N = 248; †The proportion of patients receiving each treatment is not shown as the cumulative time to intensification is shown. ‡Hazard ratio (95% confidence interval). "CV events per patient per period".
Achieved A1C goal ≤ Post-A1c minus A1c goal measured during 1 year after TI
Mean Post-TI A1c 7.7% 8.5% 8.1% — measured during 1 year after TI
Mean distance from goal network model. These proteins were considered candidates serving as in the CANA MoA molecular model overlapped with proteins in the DKD markers were measured in 296 plasma samples of the 2-year CANTATA-SU with CANA therapy and may be used to monitor CANA response. These bio-
molecular processes of disease progression. Overlapping areas in both net-
model was mapped onto an established DKD network model that describes molecular features linked to SGLT2 inhibitors from scientific literature. This CANA clinical trial. A CANA MoA network model was constructed based on diabete kidney disease (DKD). These biomarkers were then validated in a candidate biomarkers to assess in vivo how CANA may delay progression
silico potential mechanisms of action (MoA) and identified representative
The SGLT2 inhibitor canagliflozin (CANA) slows progression of kidney func-
tion decline in type 2 diabetes. In this translational study, we determined in patients without significant reduction in blood pressure. This suggests an intrinsic myocaridal action of Empagliflozin to investigate.

SGLT2i therapy significantly reduced plasma levels of TNFR-1 (9.2%, p<0.01), interleukin 6 (IL6; 26.6%, p=0.01), matrix metalloproteinase 7 (MMP7; 29.4%, p=0.01), and fibronectin 1 (FN1; 14.9%, p=0.02) during two years follow-up. Changes in TNFR-1 at 1 year independently associated with eGFR decline over 2 years (p=0.0234). This study successfully applied a network-based systems biology analysis to select biomarkers for monitoring kidney response to CANA. CANA sign-
ificantly reduced plasma levels of TNFR-1, IL6, MMP7, and FN1 suggesting CANA reverses molecular processes related to inflammation, extracellular matrix and fibrosis.

Supported By: Janssen Research & Development, LLC.

Sodium-Glucose Cotransporter 2 Inhibitors for Type 1 Diabetes Mellitus—Systematic Review and Meta-analysis
TOMOHIDE YAMADA, JUN HSUOE, NOBUHIRO SHOJIMA, TOSHIHISA YAMAI-AI, TAKASHI KADOWAKI, Tokyo, Japan
Additional treatment for type 1 diabetes is an unmet need. We investi-
gated the efficacy and safety of adding Sodium-glucose co-transporter 2 inhibitors (SGLT2i) to insulin in patients with type 1 diabetes mellitus by performing meta-analysis. Prospective randomized, placebo-controlled trials investigating insulin and SGLT2i in adults with type 1 diabetes were assessed. We searched electronic databases up to November 2017. Meta-analysis was performed by a random effects model. Two reviewers independently extracted information and evaluated study quality with the Cochran risk-of-bias tool. Among about 1300 studies identified, 14 studies were investigated [N=4,591]. Meta-analysis revealed that SGLT2i therapy significantly reduced HbA1c by 0.4% (95% confidence interval [CI]: 0.35, 0.46; P<0.001; I²=0%), fasting plasma glucose by 1.14 mmol/l (0.81, 1.47), body weight by 2.68 kg (2.0, 3.36), and systolic blood pressure by 3.37 mmHg (1.46, 5.29). In addition, the total daily insulin dose decreased by 6.0 units (4.9, 7.1), bolus insulin decreased by 3.6 units/day (2.0, 5.3), and basal insulin decreased by 4.2 units/day (2.2, 6.3). There was no significant increase of hypoglycemia or severe hypoglycemia. However, SGLT2i therapy increased diabetic ketoadiiosis [OR: 3.38 (1.74, 6.58)] and genital tract infection [OR: 3.44 (2.34, 5.07)]. In summary, SGLT2i therapy might be advantageous for type 1 diabetes. However, use of this combination should be considered carefully.

Supported By: Japan Diabetes Society; Japan Society for the Promotion of Science (16K20965); Japan Foundation for Applied Enzymology
1129-P Long-Term Efficacy and Safety of Ertugliflozin in Patients (Pts) with Type 2 Diabetes Mellitus (T2DM) Inadequately Controlled with Metformin (MET) Monotherapy—104-Week VERTIS MET Trial

SILVINA GALLO, BERNARD CHARBONNEL, ALLISON GOLDMAN, HARRY SHI, SUSAN HUYCK, AMANDA DAREKAR, BRETT LAURINDI, STEVEN TERRA, Berlin, Germany, France, Collegville, PA, New York, NY, Koninwitz, NL, Tadworth, United Kingdom, Rahway, NJ

This Phase 3 randomized, double-blind study in adults with T2DM (A1C 7.0-10.5%) on MET monotherapy (≥1500 mg/day for ≥8 weeks) included a 26 week placebo (PBO)-controlled period followed by a 78 week extension where non-responded PBO pts with fasting-finger-stick glucose ≥110 mg/dL received blinded glimepiride (GLIM). Efficacy, safety and effect on bone mineral density (BMD) of ertugliflozin (ERTU) 5 mg and 15 mg QD at week 104 are reported. Pts (N=622) had baseline mean ± SD: age 56.6 ± 8.8 y; T2DM duration 8.0 ± 6.0 y; BMI 31.1 ± 4.7 kg/m²; A1C 8.1 ± 0.9%; 41% were pre-menopausal women. At week 104, ERTU 5 mg and ERTU 15 mg reduced A1C, FPG, body weight (BW) and blood pressure (BP) compared to baseline, and increased the proportion of pts with A1C <7% (Table). Incidence of female genital mycotic infections was higher in ERTU 5 mg (7.3%; p=0.017) and 15 mg (9.8%; p=0.003) vs. PBO/GLIM (9.9%). Symptomatic hygromycia was lower in ERTU 5 mg (5.8%; p=0.009) and 15 mg (5.9%; p=0.009) vs. PBO/GLIM (13.4%). ERTU had no impact on BMD vs. PBO/GLIM, except total hip where BMD reduction was greater for ERTU 15 mg (Table). Fractures occurred in 3, 2 and 7 pts in ERTU 5 mg, 15 mg and PBO/GLIM, respectively.

ERTU added to MET in pts with inadequately controlled T2DM improved glycemic control, BW and BP over 104 weeks. ERTU was well tolerated with no clinically meaningful impact on BMD.

Table. Change in Efficacy (vs. Baseline) and Bone Mineral Density (vs. PBO/GLIM) Endpoints.

<table>
<thead>
<tr>
<th>Efficacy endpoints† (change vs. baseline)</th>
<th>ERTU 5 mg</th>
<th>ERTU 15 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from baseline at Wk 104: LS mean (95% CI)‡</td>
<td>A1C (%)</td>
<td>-0.5 (-0.6, -0.4)</td>
</tr>
<tr>
<td></td>
<td>PFS (mg/dl)</td>
<td>-17.0 (-22.7, -11.3)</td>
</tr>
<tr>
<td></td>
<td>Body weight (kg)</td>
<td>-3.6 (-4.2, -3.0)</td>
</tr>
<tr>
<td></td>
<td>SBP (mmHg)</td>
<td>-3.9 (-5.8, -2.0)</td>
</tr>
<tr>
<td></td>
<td>DBP (mmHg)</td>
<td>-2.3 (-3.6, -1.1)</td>
</tr>
<tr>
<td>Proportion of pts with A1C &lt;7%§</td>
<td>27%</td>
<td>36%</td>
</tr>
</tbody>
</table>

BMD endpoints† (change vs. PBO/GLIM)

| Percent change from baseline at Wk 104: Difference in LS mean (95% CI) vs. PBO/GLIM‡ | Lumbar spine | -0.3 (-1.1, 0.5) | -0.2 (-1.1, 0.6) |
| | Femoral neck | 0.1 (0.7, 0.9) | 0.3 (0.5, 1.1) |
| | Total hip | -0.5 (-1.1, 0.1) | -0.8 (-1.4, 0.2) |
| | Distal forearm | 0.2 (0.5, 0.9) | -0.1 (-0.8, 0.7) |

† All efficacy analyses were based on the full analysis set and excluding data after initiation of glycemic rescue therapy. 23 (11.1%), 22 (10.7%) and 51 (24.4%) pts in the ERTU 5 mg, 15 mg and PBO/GLIM groups, respectively, received glycemic rescue therapy through Wk 104 (out of all pts randomized and treated). Based on constrained longitudinal data analysis (cLDA) model with fixed effects for treatment, time, prior antihyperglycemic medication (metformin monotherapy on metformin + another antihyperglycemic medication), baseline eGFR (continuous), menopausal status (men, premenopausal women, women perimenopausal or ≥3 years postmenopausal, women ≥3 years postmenopausal) and the interaction of time by treatment. Time was treated as a categorical variable. Missing data imputed using the cLDA model fitted with fixed effects as in the primary analysis. Ten imputed values were created for each missing value. A pt with missing data was considered to have an A1C >7% if at least 6 of 10 imputed values were >7%. BMD analyses were based on raw data, and excluding data after initiation of bone rescue therapy. 1 pt in the ERTU 5 mg group and 1 pt in the ERTU 15 mg group received bone rescue.

1130-P Gemiglitin in Diabetic Kidney Disease in Asian Indians with Type 2 Diabetes in Real-Life Scenarios—Insights from Gem Study

KIRAN SHAH, SONALI A. PATANGE, ALKA P. GANDHI, Mumbai, India

Diabetic kidney disease is strongly associated with cardiovascular events, premature mortality and ESRD. Gemiglitin can be used without dose adjustment in patients with renal failure. The current study aimed to assess the possible renoprotective effects of gemiglitin, using albuminuria and eGFR as indicators. This was a multi-center real-world retrospective analysis of 146 DPP-4 inhibitor naïve type 2 diabetic patients with established moderate DKD (eGFR between 30 to 45 ml/min/1.73m² for ≥3 months) with diabetic retinopathy who received gemiglitin 50 mg once daily for ≥24 weeks in addition to anti-hyperglycemic, anti-hypertensives and statins. Goodness of fit was examined using SPSS statistics 20 and ANOVA was conducted to interpret the results. Results: Baseline characteristics were: 71 (48.6%) males and 75 (51.4%) females, the mean age was 60.81 ± 7.42 years, mean duration was 11.92 ± 3.3 years, mean BMI was 26.54 ± 2.59 kg/m². Gemiglitin showed significant improvements in glycaemia, renal and lipid parameters with no deterioration in retinopathy, liver enzymes and with no hypoglycemic episodes and was weight neutral. In the present study, gemiglitin reduced albuminuria independent of age, gender, duration of diabetes, Hba1c, eGFR and SBP. It could ameliorate diabetic nephropathy by reducing urine albumin excretion and mitigating the reduction of eGFR in diabetic patients.

Table. Changes in Glycemic and Renal Parameters at Week 24 vs. Baseline.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>At Baseline (n=146)</th>
<th>At 24 Weeks (n=146)</th>
<th>% change from Baseline to 24 Weeks</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBS (mg/dL)</td>
<td>192.90 ± 53.46</td>
<td>129.99 ± 19.46</td>
<td>31.6%</td>
<td>Significant (p&lt;0.001)</td>
</tr>
<tr>
<td>PPBS (mg/dL)</td>
<td>248.72 ± 62.75</td>
<td>170.55 ± 23.00</td>
<td>31.4%</td>
<td>Significant (p&lt;0.001)</td>
</tr>
<tr>
<td>Hba1c (%)</td>
<td>9.22 ± 1.51</td>
<td>7.88 ± 0.57</td>
<td>1.5%</td>
<td>Significant (p&lt;0.001)</td>
</tr>
<tr>
<td>UACR (mg/g)</td>
<td>380.61 ± 77.17</td>
<td>228.36 ± 46.05</td>
<td>25%</td>
<td>Significant (p&lt;0.001)</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>521.2 ± 62.2</td>
<td>388.8 ± 34.3</td>
<td>31.4%</td>
<td>Significant (p&lt;0.001)</td>
</tr>
<tr>
<td>eGFR (ml/min)</td>
<td>73.7 ± 5.86</td>
<td>71.5 ± 5.52</td>
<td>12%</td>
<td>Significant (p&lt;0.001)</td>
</tr>
</tbody>
</table>

Table. Changes in Glycemic and Renal Parameters at Week 24 vs. Baseline.

A Phase 3 Study to Assess the Efficacy and Safety of Ipragliflozin in Russian Patients with Type 2 Diabetes Mellitus Inadequately Controlled by Metformin

MARINA V. SHESTAKOVA, JOHN P. WILDING, WIM WILPSHAAR, REINER N. TRETTER, VALERIA L. ORLOVA, ANDREY F. VERBOVOY, Moscow, Russian Federation, Liverpool, United Kingdom, Leiden, Netherlands, Saint Petersburg, Russian Federation, Samara, Russian Federation

Aim: To assess the efficacy and safety of ipragliflozin as add-on therapy to metformin in Russian patients with T2DM.

Methods: In this double-blind trial conducted in 14 centers in Russia, 165 patients were randomized 2:1 to ipragliflozin (50 mg/day) or placebo for 24 weeks while continuing metformin. Patients who had Hba1c ≥7.0% at Week 12 received open-label ipragliflozin (50 mg/day) in addition to the blinded drug from Week 12-24.

Results: Significant reductions in Hba1c and body weight from baseline to Week 12 in favor of ipragliflozin were observed; the incidence of AEs was similar in both groups (Table). Hba1c and weight improvements were sustained from Week 12-24 in patients who remained on 50 mg ipragliflozin (mean change from Week 12: 0.16% and -0.49 kg, respectively; p<0.05). Up titration to 100 mg ipragliflozin led to a further reduction in body weight (mean change from Week 12: -0.65 kg, p=0.004) and an additional 13% (9/69) achieving Hba1c <7% at Week 24. Incidence of AEs was similar in 50 mg (23.7%) and 100 mg groups (24.8%). No clinically significant changes in vital signs were noted during the study.

Conclusion: 50 mg Ipragliflozin added to metformin significantly reduced Hba1c and body weight after 12 weeks and showed a comparable safety profile as placebo. Up titration to 100 mg/day conferred added benefits with no additional safety concerns.
**Table. Efficacy and AE Results from Baseline to Week 12**

<table>
<thead>
<tr>
<th>Dose (N)</th>
<th>Baseline</th>
<th>Iprag/Placebo</th>
<th>EOT Week 12</th>
<th>Change</th>
<th>*Adjusted mean difference (95% CI)</th>
<th>*p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg (519)</td>
<td>8.4 (8.94)</td>
<td>7.38 (8.30)</td>
<td>-1.01 (0.89)</td>
<td>-0.26 (0.30)</td>
<td>0.049</td>
<td></td>
</tr>
<tr>
<td>15 mg (374)</td>
<td>-0.9 (-1.0)</td>
<td>-1.79 (2.12)</td>
<td>0.24 (0.06)</td>
<td>-0.45 (-0.61)</td>
<td>0.007</td>
<td></td>
</tr>
</tbody>
</table>

**Safety endpoints (SAE)**

| Drug-related AEs (N) | — | 12 (15) | 1 (3) | — | — |

*ANCVA model with treatment as fixed effect, center as random effect, and baseline value as covariate. Data are presented as mean (SD) unless stated otherwise. Iprag/Placebo (PBO) = 100; SAF = 100 and placebo (PBO or SAF = 50). AEs, adverse events; EOT, end of treatment; EOT, full analysis set; Iprag, ipragliflozin; SAF, safety analysis set.

**Supported By:** Astellas Pharma Inc.

**1132-P Efficacy and Safety of SGLT2 Inhibitor across Racial Groups in Patients with Type 2 Diabetes Mellitus (T2DM)**

JIE LIU, LISA TARASENKO, ANNPEY PONG, SUSAN HUYCK, LARRY WU, JAMES P. MANCUSO, STEVEN TERRA, BRETT LAURING, Railway, NJ, New York, NY, Kenilworth, NJ, Groton, CT, Andover, MA

SGLT2 inhibition (ERTU) is a sodium-glucose cotransporter 2 (SGLT2) inhibitor for the treatment of T2DM. Pharmocokinetic analysis indicates ERTU plasma exposure is not affected by race. The efficacy and safety of ERTU by race was assessed in pooled analyses from 3 randomized, double-blind, placebo (PBO)-controlled, Phase 3 trials. Patients received ERTU 5 mg, 15 mg or PBO for 26 weeks. Least-squares (LS) means for change from baseline to Week 26 were calculated for hemoglobin A1C (A1C), body weight (BW) and systolic blood pressure (SBP). General and prespecified adverse events (AEs) were evaluated.

The analysis included 1544 patients (white 73%; black 7%; Asian 15%; other 5%). Baseline demographics and characteristics were generally similar across treatment groups and racial groups, except lower mean BW and BMI in Asians. No notable differences in A1C, BW and SBP reductions were observed across racial groups (Table 1), except for greater SBP reduction observed in blacks. Across racial groups there were no notable differences in general AEs with ERTU vs. PBO. An increase in genital mycotic infections was seen with ERTU vs. PBO across all racial groups. Precision of between-treatment effects was limited in blacks, Asians and others due to small group size.

ERTU efficacy and safety was generally similar across racial groups although a greater reduction in SBP was observed in blacks.

**1134-P Which Is Better? High-Dose Metformin Alone or Combination of Low-Dose Metformin and Linagliptin on Glycemic Variability in Japanese Type 2 Diabetes Patients with Insufficient Glycemic Control with Low-Dose Metformin Alone—A Randomized, Crossover, Pilot Study**

HIROSHI TAKAHASHI, RIMEI NISHIMURA, KAZUNORI UTSUNOMIYA, Tokyo, Japan

The aim of this study is to investigate the effect of high dose metformin or combination of low dose metformin and linagliptin on glycemic variability (GV) in Japanese type 2 diabetes (T2D) patients with insufficient glycemic control with low dose metformin alone in a cross-over study using continuous glucose monitoring (CGM). This study was conducted in T2D outpatients (7% < HbA1c < 10%) receiving low dose metformin (750-1000 mg) alone. All patients were assigned to metformin 1500 mg monotherapy (high dose metformin; HMET) or combination of metformin 750 mg and linagliptin 5 mg (low dose metformin and DPP-4; LMET+DPP-4) in a cross-over fashion and underwent CGM assessments more than 4 weeks after change of treatment. 24-hour data were collected for comparison after they had had the same retort pouch foods. Mean glucose level, standard deviations of glucose (SD), glucose coefficient of variation (%CV), mean amplitude of glucose excursions (MAGE), pre-meal glucose levels, and 3-hour postprandial glucose area under the curve (AUC, >160 mg/dL) were compared between HMET and LMET+DPP-4 groups by using t-test. The study enrolled a total of 11 patients with T2D [men/women, 8/3; age, 51.9 ± 9.8 years; BMI, 26.3 ± 3.0 kg/m²; HbA1c, 7.8 ± 0.4%; and metformin dose 750-1000 mg, 8/5]. Of the CGM-derived GV metrics for the HMET vs. LMET+DPP-4, mean glucose level, SD, MAGE and %CV were not significantly different (p=0.34, 0.39, 0.86, 0.28). Again, while the pre-breakfast glucose level were not significantly different between the groups (p=0.43), the AUC after breakfast was significantly smaller in LMET+DPP-4 vs. HMET (5004 ± 3220 vs. 7712 ± 5177; p=0.047). A comparison of GV with HMET vs. LMET+DPP-4 suggested that LMET+DPP-4 may reduce post-breakfast GV to a greater degree than HMET in Japanese patients with T2D receiving low dose monotherapy.
Apabetalone (RVX-208) Lowers Major Adverse Cardiovascular Events (MACE) in Diabetes Mellitus Patients with CVD by Attenuating Monocyte Adhesion to Endothelial Cells

LAURA TSUJIKAWA, EWELENA KULIKOWSKI, CYRUS CALOSING, SYLWIA WASIAK, DEAN GILHAM, CHARLOTTE GRANHALL, CILIE W. HANSEN, AZADEH HOUSHMAND-OREGAARD, ANDREAS BÔRSTING JORDY, ASTRID BREITSCHAFT, ERIK CHRISTIANSEN, ANDREAS BÔRSTING JORDY, ASTRID BREITSCHAFT, ERIK CHRISTIANSEN, Søborg

In summary, Apabetalone inhibits HG and TMAO enhanced adhesion of THP-1 to HUVECs, this process mimics a step in CVD pathogenesis. RVX-208 suppresses cellular adhesion genes; VLA-4 in THP-1 and both E-selectin plus MYD88 in HUVECs. BETi blocks TMAO activity and its production by inhibiting FXR expression, a regulator of FMO3 gene transcription. Rapid actions of BETi in dissociating BRD4 from FXR DNA suggests a direct effect of RVX-208 on transcription of this gene.

Duodenal Mucosal Resurfacing Elicits Improvement in Glycemic and Hepatic Parameters in Type 2 Diabetes—One-Year Multicenter Study Results

ANNEKE C.G. VAN BAAR, MAX NIEUWDORP, FRITS HOLLEMAN, JACQUES DEVIERE, LAURENT CRENIER, REHAN HAIERY, RACHEL L. BATTERHAM, DAVID HÖKINS, LEONARDO RODRIGUEZ GRUNERT, MANDEL GALVAD NETO, PAULINA VIGNOLO, GUIDI COSTAMAGNA, JACQUES J. BERGMAN, AMSTERDAM, NETHERLANDS, BRUSSELS, BELGIUM, LONDON, UNITED KINGDOM, SANTIAGO, CHILE, MIAMI, FL, ROME, ITALY

Aims: Duodenal Mucosal Resurfacing (DMR) is a novel endoscopic procedure which has been shown to improve glycemic control at 6 months in type 2 diabetes (T2D). It is thought to exert insulin-sensitizing effects. DMR entails catheter based circumferential mucosal lifting followed by hydrothermal ablation. This study aimed to extend DMR experience, determining efficacy over 12 months in T2D patients on stable oral glucose lowering treatment.

Methods: Single arm, multicenter study. 46 T2D patients on oral glucose lowering medication received a DMR procedure. Impact on glycemic control (HbA1c and fasting plasma glucose), insulin resistance (HOMA-IR) and liver enzymes (AST and ALT) was determined at baseline and 1, 3, 6, 9, 12 mo post DMR. Glucose lowering medication was kept stable 6 mo post DMR and adjusted according to local guidelines thereafter.

Results: See Figure 1. At 12 mo: ΔHbA1c -1.0±0.2% (p ≤ 0.001), ΔFGP -41±8 mg/dL (p ≤ 0.001), ΔHOMA-IR -3.6±0.9 (p ≤ 0.001). A weight -2.7±0.6kg (p ≤ 0.003), ΔALT -10±4 (p = 0.005) and ΔAALT -6±2 (p=0.002). DMR was well tolerated with no related serious adverse events or unexpected adverse device events reported.

Conclusions: Single DMR treatment elicited significant and clinically relevant reductions in glycemic and hepatic parameters that were sustained at 12 months, suggesting considerable potential of DMR for the treatment of T2D.
Comparison of the Effect of Empagliflozin and Glimepiride on the Endothelial Function in Patients with Type 2 Diabetes—A Randomized Study

HARUKA TAMURA, YOSHINOBU KONDO, KOHEI ITO, SHINOBU SATOH, YASUO FERAUCHI, Chibasaki, Japan, Yokohama, Japan

Reportedly, patients with type 2 diabetes at a high risk for cardiovascular events receiving empagliflozin, compared with placebo, have a lower rate of the primary composite cardiovascular outcome and death from any cause.

This study compares the effect of empagliflozin and glimepiride on the endothelial function in patients with type 2 diabetes by flow-mediated dilatation (FMD). This prospective, randomized, parallel-group comparison study enrolled 31 patients who were continuously treated with metformin and glargine before bedtime for 12 weeks, followed by the random addition of 16-mg empagliflozin (empagliflozin group, n = 13) or 0.5-mg glimepiride (glimepiride group, n = 18) for 12 weeks. FMD was assessed before and after additional treatment. The primary outcome was a change in FMD (ΔFMD) with additional treatment before and after 12 weeks. The key secondary outcomes were changes in HbA1c, GA, FPG, body weight, LDL-C, and systolic and diastolic blood pressures.

No significant difference existed in age, HbA1c, FMD, and doses of metformin and glimepiride, and ΔFMD had no significant difference (empagliflozin, −0.79% ± 1.35%; glimepiride, −0.62% ± 2.78%; P = 0.84). Although HbA1c of both groups improved significantly, the change was not statistically significant. The body weight increased only in the glimepiride group (baseline, 69.6 ± 14.5 kg; 12 weeks later, +1.17 ± 1.99 kg; P = 0.02), but the change was not statistically significant. Likewise, changes in GA, FPG, LDL-C, and systolic and diastolic blood pressures were not significant.

In conclusion, empagliflozin besides metformin and glargine did not affect the endothelial function significantly compared with glimepiride in patients with type 2 diabetes. In empagliflozin group, body weight was not changed significantly for 12 weeks. Insulin usage may affect body weight, and that may affect these results. The effect of empagliflozin on endothelial function was not clear in this study.

1139-P

Mortality Risk of Noninsulin Glucose-Lowering Drugs in Type 2 Diabetes—A Network Meta-analysis of Observational Trials

BRENDA BONGAERTS, LENA M. LINDNER, ANNIKA HOYER, OLIVER KUSS, CHRISTIAN HEBER, HADI AL-HASANI, SR., KRISTEN MÜSSIG, MICHAEL RÖDEN, WOLFGANG RATHMANN, Düsseldorf, Germany

Given the short-comings of randomized controlled trials, such as low numbers of patients and events, we aimed to perform a network meta-analysis of observational trials on the effects of noninsulin glucose-lowering drugs on all-cause and cardiovascular mortality in type 2 diabetes.

We searched MEDLINE and EMBASE through August 2017. From the 38 eligible studies, we extracted patient characteristics, exposure, outcome, confounder-adjusted effect measures, and risk of bias. All-cause and cardiovascular mortality risk were assessed with random-effects network meta-analysis.

In 32 studies reporting on all-cause mortality (1,661,945 persons) and in 11 studies on cardiovascular mortality (358,784 persons), 119,591 (7.2%) and 9,221 (2.6%) persons, respectively, died during follow-up. Compared to metformin, sulfonylurea drugs (SU) increased all-cause mortality risk (HR: 1.42 (95% CI: 1.29–1.56)). Dipeptidyl peptidase-4 inhibitors (DPP4i) added to metformin significantly decreased all-cause mortality risk compared to metformin monotherapy (HR: 0.76 (0.63–0.93)), any other drug class as monotherapy, and SU + metformin dual therapy (HR: 0.69 (0.60–0.79)). DPP4i + metformin dual therapy was associated with even larger reductions in risk of cardiovascular mortality; HR: 0.40 (0.21–0.79) when compared to metformin monotherapy, and HR: 0.41 (0.23–0.74) when compared to SU + metformin dual therapy. Glucagon-like-peptide-1 receptor agonists + metformin dual therapy tended to, but did not significantly, decrease mortality risk when compared to metformin monotherapy (all-cause mortality. HR: 0.98 (0.53–1.47); cardiovascular mortality, HR: 0.74 (0.30–1.32)).

In conclusion, this large network meta-analysis evidently confirmed that SU, compared to metformin, increased all-cause mortality risk. DPP4i + metformin dual therapy, compared to other treatments, resulted in a consistent risk reduction of both all-cause and cardiovascular mortality.

A Pooled Analysis of the Efficacy and Safety of Ertugliflozin as Add-On Therapy to Metformin

ROBERTO A. CALLE, JIE LIU, SUSAN HUYCK, LARRY WU, ANNPEY PONG, JAMES P. MANCUSO, STEVEN TERRA, BRETT LAURING, Cambridge, MA, Kenilworth, NJ, Groton, CT, Andover, MA

Ertugliflozin (ERTU) is a highly selective sodium-glucose cotransporter 2 inhibitor in development for treatment of patients with type 2 diabetes mellitus (T2DM). This pooled analysis characterized the efficacy and safety of ERTU when used as add-on therapy to metformin (MET).

Pooled data from 2 randomized, double-blind, placebo-controlled Phase 3 studies with similar design and patient population (NCT02033889) (VERTIS MET), NCT02036515 (VERTIS SITA2) were analyzed. Adult patients with T2DM inadequately controlled on MET (a sitagliptin) with A1C ≥7.0 to ≤10.5% were randomized to placebo (PBO), ERTU 5 mg or 15 mg for 26 weeks.

Mean baseline (BL) characteristics of patients (N=1083) were similar across pooled treatment groups (age 57.7 years; T2DM duration 8.6 years; A1C 8.1%; body weight [BW] 85.7 kg; systolic blood pressure [SBP] 130.6 mmHg; estimated glomerular filtration rate 89.4 mL/min/1.73 m²). Changes in A1C, BW and SBP after 26 weeks are shown in the Table. Relative to PBO, more patients receiving ERTU had A1C <7.0%, BW reduction of ≥5%, or SBP <130 mmHg (among patients with BL SBP ≥130 mmHg) at Week 26. ERTU had an overall similar safety profile to PBO, except for a higher incidence of adverse events (AEs) of genital mycotic infections and of AEs related to osmotic diuresis.

Addition of ERTU to MET (a sitagliptin) provides reductions in A1C, BW and SBP, resulting in more patients achieving metabolic treatment goals.

Table. Changes from Baseline in A1C, BW and SBP at Week 26.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo (n=362)</th>
<th>Ertugliflozin 5 mg (n=363)</th>
<th>Ertugliflozin 15 mg (n=363)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Least squares mean change from baseline in A1C at Week 26 (95% CI), %</td>
<td>-4.1 (-2.0, 0.0)</td>
<td>-4.9 (-3.0, -2.8)</td>
<td>-5.0 (-3.0, -3.0)</td>
</tr>
<tr>
<td>Placebo-adjusted difference</td>
<td>—</td>
<td>-0.9 (0.0, -0.8)</td>
<td>-1.0 (0.0, -0.8)</td>
</tr>
<tr>
<td>Patients with A1C&lt;7.0% at Week 26, n (%)</td>
<td>59 (16.3)</td>
<td>123 (33.9)</td>
<td>143 (39.9)</td>
</tr>
<tr>
<td>Least squares mean change from baseline in BW at Week 26 (95% CI), kg</td>
<td>-1.3 (-1.6, -1.0)</td>
<td>-2.1 (-2.4, -1.8)</td>
<td>-2.3 (-2.6, -2.0)</td>
</tr>
<tr>
<td>Placebo-adjusted difference</td>
<td>—</td>
<td>-0.8 (-1.2, -0.4)</td>
<td>-1.2 (-1.7, -0.7)</td>
</tr>
<tr>
<td>Patients with BW reduction ≥5% at Week 26, n (%)</td>
<td>39 (10.8)</td>
<td>115 (31.7)</td>
<td>103 (28.8)</td>
</tr>
<tr>
<td>Least squares mean change from baseline in SBP at Week 26 (95% CI), mmHg</td>
<td>-0.8 (-2.0, 0.3)</td>
<td>-4.1 (-3.3, -2.8)</td>
<td>-4.9 (-3.1, -2.7)</td>
</tr>
<tr>
<td>Placebo-adjusted difference</td>
<td>—</td>
<td>-1.0 (-1.5, -0.5)</td>
<td>-1.8 (-2.5, -1.1)</td>
</tr>
<tr>
<td>Patients with BW reduction ≥5% at Week 26, n (%)</td>
<td>30 (8.5)</td>
<td>77 (21.3)</td>
<td>70 (19.6)</td>
</tr>
</tbody>
</table>

Supported By: Merck Sharp & Dohme Corp, Pfizer Inc.
substantial differences in patient characteristics among those who were prescribed an SGLT2i before or after EMPA-REG: 10.4% (before) and 14.4% (after) of patients had a history of macrovascular complications, compared with 12.9% of patients prescribed a different class of medication (p = 0.24).

At baseline (initiation of second-line therapy), the proportion of patients who received an SGLT2i was higher when the initiation occurred after vs. before EMPA-REG (8.4% vs. 5.9%, p < 0.001).

Conclusions: The overall proportion of patients prescribed an SGLT2i was low, but varied greatly across countries. SGLT2i use increased modestly after EMPA-REG. Although the CV benefits of SGLT2 use have been best demonstrated in people with established macrovascular disease, the clinical decision to prescribe these agents does not appear to be primarily driven by the presence of macrovascular complications.

Supported By: AstraZeneca

### 1142-P

**Safety and Efficacy of Sitagliptin (SITA) Compared with Dapa-gliptozin (DAPA) in Subjects with T2D, Mild Renal Impairment, and Inadequate Glycemic Control on Metformin (MET) ± a Sulfonylurea (SU)**

RUSSELL S. SCOTT, JERRY D. MORGAN, ZACHARY ZIMMER, RAYMOND L.H. LAM, EDWARD A. O’NEILL, KEITH D. KAUFMAN, SAMUEL S. ENGEL, ANNASWAMY RAJI, CHRISTCHURCH, New Zealand, Kenilworth, NJ, Rajway, NJ

While choice of AHAs may be modified in patients with T2D and moderate or severe renal insufficiency, this is generally not the case in patients with mild renal insufficiency. Clinical trial data focused on this population, which represents ~40% of patients with T2D, are lacking.

In a randomized, double-blind, active comparator-controlled clinical trial, the safety and efficacy of adding SITA (100 mg qd) or DAPA (10 mg qd) to treatment of patients with eGFR ≥60 and <90 mL/min/1.73 m² and A1C ≥7.0% and <9.5% while on MET ± SU were assessed. The primary efficacy endpoint was change from baseline A1C at Week 24 (analyzed with a constrained longitudinal data analysis model), with a primary hypothesis of non-inferiority of SITA to DAPA, based on the prespecified criterion of the upper bound of the between-treatment difference 95% CI (SITA minus DAPA) ≤0.5% if the upper bound was <0.0%, SITA would be declared superior.

The overall proportion of patients prescribed an SGLT2i was 65.4% (445/680) during Phases 1 + 2.

**Table.**

<table>
<thead>
<tr>
<th>A1C Goal Achieved (%)</th>
<th>MET/SITA, N = 307</th>
<th>DAPA, N = 306</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 7.5%</td>
<td>60.7% (189/312)</td>
<td>31.8% (97/306)</td>
<td>1.8 (1.39, 2.38)</td>
</tr>
<tr>
<td>≥ 7.0%</td>
<td>91.4% (278/305)</td>
<td>75.9% (235/306)</td>
<td>1.8 (1.39, 2.38)</td>
</tr>
</tbody>
</table>

**Results:**

- **Baseline A1C 7.0%‑7.5%:**
  - ≥ 6.5%: 74.1% (43/58) vs. 44.8% (26/58), p = 0.006
- **Baseline A1C 8.0%‑8.5%:**
  - < 6.5%: 46.5% (47/101) vs. 17.4% (16/92), p = 0.006
- **Baseline A1C 9.0%‑9.5%:**
  - < 6.5%: 52.4% (27/52) vs. 32.9% (27/82), p = 0.006
- **Baseline A1C 10.0%‑10.5%:**
  - < 6.5%: 46.5% (47/101) vs. 32.9% (27/82), p = 0.006

**Safety and Tolerability:**

- Safety and tolerability were similar with SITA and DAPA, with summary AE profiles being otherwise similar.

**Conclusion:**

SITA treatment over 24 weeks resulted in greater glycemic efficacy and greater % of patients at A1C goal than DAPA in patients with T2D and mild renal impairment who were inadequately controlled on MET ± SU.

Supported By: Merck & Co., Inc.

### 1143-P

**A1C Goal Attainment with Initial Dual Therapy with Metformin (MET)/Sitagliptin (SITA) Compared with Met Monotherapy—Impact of Baseline A1C and Target A1C**

ANNASWAMY RAJI, MISSO C. ELLISON, RAYMOND L.H. LAM, EDWARD A. O’NEILL, SAMUEL S. ENGEL, KENILWORTH, NJ

While MET is generally recommended as initial pharmacologic therapy for T2D, the substantial proportion of patients who do not achieve glycemic targets with monotherapy argues for initial use of dual therapy in patients with high A1C levels (e.g., >7.5% per AACE and >9.0% per ADA guidelines). The individualization of glycemic targets based on patient characteristics adds an additional complexity to treatment decision-making. This analysis was designed to identify the baseline A1C range from which patients benefitted the most with initial dual therapy (compared with monotherapy) across a range of A1C goals.

Data from 3 randomized clinical trials containing treatment arms of both initial MET monotherapy (1700-2000 mg qd, n=778) and initial MET + SITA dual therapy (1700-2000 mg + 100 mg qd, n=289) were pooled. Patients in all 3 trials had an entry A1C of at least 7.5% (mean = 9.4% in both groups).

Demographic and disease-related baseline characteristics were well balanced in both groups. Rates of achieving various A1C goals after 18-24 weeks of treatment were assessed across a range of baseline A1C, and odds ratios for goal attainment were calculated (Table).

**Table.**

<table>
<thead>
<tr>
<th>A1C Goal Achieved (%)</th>
<th>MET/SITA, N = 398</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 7.5%</td>
<td>60.7% (57/94)</td>
<td>1.8 (1.39, 2.38)</td>
</tr>
<tr>
<td>≥ 7.0%</td>
<td>91.4% (94/103)</td>
<td>1.8 (1.39, 2.38)</td>
</tr>
</tbody>
</table>

**Table:**

<table>
<thead>
<tr>
<th>Baseline A1C 7.0%‑7.5%</th>
<th>Goal achieved, % (n/n) MET/SITA, N = 398</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6.5%</td>
<td>74.1% (43/58)</td>
<td>1.8 (1.39, 2.38)</td>
</tr>
<tr>
<td>≥ 7.0%</td>
<td>91.4% (53/58)</td>
<td>1.8 (1.39, 2.38)</td>
</tr>
</tbody>
</table>

**Conclusion:**

SITA treatment over 24 weeks resulted in greater glycemic efficacy and greater % of patients at A1C goal than DAPA in patients with T2D and mild renal impairment who were inadequately controlled on MET ± SU.

Supported By: Merck & Co., Inc.

### 1144-P

**Efficacy and Safety of Sitagliptin (SITA) ‑Based Dual and Triple Combination Therapy in Older Chinese People with T2D**

XIANGYANG LIU, LI WANG, YING XING, SAMUEL S. ENGEL, GUOJUAN CHEN, YE ZHANG, RUYA ZHANG, SHU LIU, JIANGPING WENG, QIUHE JI, XI’an, China, Kenilworth, NJ, Shanghai, China, Beijing, China, Guangzhou, China

Despite increasing prevalence of T2D in older Chinese people, no studies have evaluated the efficacy and safety of DPP-4 inhibitor-based combination therapy in this population. In the STRATEGY Study (a multicenter, randomized, active-controlled, open-label clinical trial in Chinese people with T2D), patients were treated for 20 weeks with a combination of SITA and metformin (MET) (Phase 1). Those with A1C ≥7.0% and <10.0% at Week 16 were randomly assigned at Week 20 to 1 of 4 additional AHAs and continued treatment for another 24 weeks (Phase 2). Here we report efficacy and safety in the 881 patients aged ≥65 year.

At baseline, the mean age, duration of diabetes, BMI and A1C of the analyte group were 75 year, 25 kg/m² and 7.7%, respectively; half were male. Changes in A1C were 44.9% (S05/S60) during Phase 1, and 65.4% (S45/S60) during Phases 1 + 2.

Through Week 20/n=881 and Week 44/n=269, the incidences of any adverse events (AEs) were 30% and 31%, of drug-related AEs were 4%.

Supported By: AstraZeneca
and 5%, and of serious AEs were 2% and 3%, respectively. Hypoglycemia incidences were highest with glimepiride and gliclazide (Table); no severe hypoglycemia was reported.

In older Chinese people, dual and triple combination therapy based on SITA and MET provided clinically meaningful improvement in glycemic control and was generally well tolerated.

### Table

#### Phase 1 (Baseline through Week 20)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>A1C Mean ± SD, %</th>
<th>Change from Baseline A1C to Week 16, %</th>
<th>Hypoglycemia, % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SITA + MET, N = 606</td>
<td>7.94 ± 0.78</td>
<td>-0.81 ± 0.82</td>
<td>4.3% (24/691)</td>
</tr>
</tbody>
</table>

#### Phase 2 (Weeks 20 through 44)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>A1C Mean ± SD, %</th>
<th>Change from Baseline A1C to Week 24, %</th>
<th>Hypoglycemia, % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SITA + MET + glimepiride, n = 63</td>
<td>7.62 ± 0.82</td>
<td>-0.73 ± 0.87</td>
<td>9.6% (6/73)</td>
</tr>
<tr>
<td>SITA + MET + gliclazide, n = 69</td>
<td>7.88 ± 0.76</td>
<td>-0.65 ± 0.77</td>
<td>10.5% (7/65)</td>
</tr>
<tr>
<td>SITA + MET + repaglinide, n = 47</td>
<td>7.69 ± 0.70</td>
<td>-0.54 ± 0.78</td>
<td>5.9% (3/51)</td>
</tr>
<tr>
<td>SITA + MET + acarbose, n = 64</td>
<td>7.59 ± 0.89</td>
<td>-0.46 ± 0.73</td>
<td>1.5% (1/64)</td>
</tr>
</tbody>
</table>

*Supported by Meck & Co, Inc.*

### Evaluation of Fractures, Bone Mineral Density (BMD), and Bone Biomarkers in Patients with Type 2 Diabetes Mellitus (T2DM) Receiving Ertugliflozin

MARY A. HICKMAN, ROBERT FREDERICH, SHRITA M. PATEL, SILVINA GALLO, BRETT LAURING, STEVEN TERRA, SUSAN L. JOHNSON, URSZULA MASLIUKIEWICZ, SUSAN HYUCK, JAMES P. MANCUSO, Grono, CT, Collegville, PA, North Wales, PA, Berlin, Germany, Rahway, NJ, Andover, MA, Dartmouth, NJ, Kenilworth, NJ

Ertugliflozin (ERTU) is an SGLT2 inhibitor for the treatment of T2DM. The risk of fracture was assessed in adults with T2DM receiving ERTU relative to placebo (PBO) or active comparator in pooled analyses of 7 randomized, double-blind, Phase 3 trials. Patients (N=4859) received ERTU 5 mg (n=1716), ERTU 15 mg (n=1683) or non-ERTU (PBO, glimepiride or sitagliptin; n=1450) for up to 2 years (years). Mean age was 57.8 years, 25.8% were 65 years old and 51.8% were male. Mean eGFR was 85.3 mL/min/1.73 m^2_.

At week 104, there were no meaningful differences from baseline in procollagen type 1 N-terminal propeptide (P1NP; ERTU 5 mg 10.1%; ERTU 15 mg 0.5%; non-ERTU 0.6%).

At week 26, serum calcium did not change when compared across groups similar across groups (ERTU 5 mg 0.5%; ERTU 15 mg 0.5%; non-ERTU 0.6%)

### 1147-P

**Development of an Innovative Screening Tool and Identification of Novel β-Cell Protective Drugs**

SMITHTHAMI SITHARA, BHAVISHA PATEL, MEGAN K. ELLIS, TAMSYN CROWLEY, KEN WALDER, KATHRYN AUSTON-MOURNEY, Woon Ponds, Australia

Type 2 diabetes (T2D) is characterised by progressive β-cell failure. While many drugs assist in the management of diabetes, current treatments cannot stop or slow the progression of this failure. In fact, over 50% of people with T2D have poor glycaemic control despite best practice management. Thus a key tool in T2D management would be the development of new drugs that restore adequate insulin secretion, but also protect against the continuous deterioration of the β-cells. Previous drug discovery techniques have focused on single targets or pathways, however because β-cell dysfunction is extremely complex, targeting one pathway has proven to be ineffective. One approach that encompasses the intricacy of complex disease is that of gene expression signatures (GES) which have proved to be a valuable tool in other complex diseases. In this study, we developed a β-cell model consisting of three different conditions: 1) normal function/viability (“healthy”), 2) dysfunction/reduced viability (“diabetic”) and 3) successful treatment of dysfunction/reduced viability with a cocktail of known drugs (selected based on their ability to treat different aspects of β-cell dysfunction, “suc cessfully treated”). We then used a comprehensive screening approach using gene expression profiles under these three conditions to generate a β-cell GES consisting of a gene set that robustly and accurately reflects the overall state of the cell. This GES was then used to screen a library of off-patent compounds, with known safety profiles, and the 12 top candidate compounds identified. In vitro testing of these drugs identified that nine significantly improved beta-cell function and survival. Therefore, we have developed a novel platform for T2D β-cell drug discovery and identified several candidate compounds that could prevent the progressive failure of β-cells. These drugs have the potential to be powerful T2D treatments and thereby reduce the burden of T2D and improve quality of life for millions worldwide.

*Supported By: Deakin University, Geelong Community Foundation; Sir Edward Dunlop Medical Research Foundation*
1149-P
Triple vs. Dual Therapy with Low-Dose Dapagliflozin plus Saxagliptin vs. Each Monocomponent Added to Metformin in Uncontrolled Type 2 Diabetes

JULIO ROSENSTOCK, SHIRA PERL, EVA K. JOHNSSON, STEPHEN JACOB, Dallas, TX, Gothenburg, MD, Malmö, Sweden, Vilnius, Germany

Triple therapy with dapagliflozin (DAPA) 10 mg/d + saxagliptin (SAXA) 5 mg/d added to metformin (MET) has greater efficacy than dual therapy in type 2 diabetes (T2D) inadequately controlled by MET alone. We tested triple therapy with the lower starting dose of DAPA in a randomized, parallel-group, double-blind, 24-week trial (NCT02681094) to evaluate the efficacy and safety of DAPA 5 mg/d + SAXA 5 mg/d add-on therapy vs. add-on of either agent in patients with T2D (AIC 7.5%–10%) uncontrolled with stable MET 1500 mg/d monotherapy. The primary end point was change in AIC from baseline to week 24; secondary end points were the proportion of participants achieving AIC <7% at week 24 and changes in FPG and body weight from baseline to week 24. At baseline, mean±SD patient characteristics were similar in all arms: age, 56.3±10.5 years; AIC, 8.2±0.3%; BMI, 31.9±5.4 kg/m²; T2D duration, 7.6±6.1 years. Triple therapy resulted in significant decreases in AIC and FPG vs. both dual therapies, and reduced body weight vs. SAXA + MET (Table). Incidences of genital infections were 3.4%, 1.7% and 0%, urinary tract infections 3.1%, 2.0% and 2.4%, hypoglycemia 5.6%, 2.7% and 3.4% for DAPA + SAXA + MET, DAPA + MET and SAXA + MET, respectively.

In conclusion, DAPA 5 mg/d + SAXA 5 mg/d added to MET led to greater improvement in glycemic control vs. either agent added to MET in T2D uncontrolled with MET monotherapy.

1150-P
Safety and Tolerability of Empagliflozin in East Asian Patients with Type 2 Diabetes—Pooled Analysis of Phase I–III Clinical Trials

ATSUTAKA YASUI, DAISUKE YABE, LINONG JI, MOON-KYU LEE, RONALD C. MA, TIE-NJUEN CHANG, TOMOUDI OKAMURA, CORDULA ZELLER, STEFAN KASPERS, JOSSE LEE, SVIN KOHLER, YUTAKA SEINO, Tokyo, Japan, Kobe, Japan, Beijing, China, Seoul, Republic of Korea, Hong Kong, China, Taipei, Taiwan, Biberach, Germany, Ingelheim, Germany, Osaka, Japan

Aims/Introduction: As the pathophysiology of type 2 diabetes (T2DM) differs in East Asian patients compared with that in other ethnic groups, a comprehensive evaluation of the safety of empagliflozin (EMPA) in East Asian patients is desirable to inform clinical practice in the patient population. We therefore investigated the safety and tolerability of EMPA in East Asian patients with T2DM.

Materials and Methods: Data were pooled from patients with T2DM treated with placebo, EMPA 10 mg or 25 mg in 15 Phase I–III trials plus 4 extension studies. Adverse events (AEs) were analyzed in the subgroup of patients from East Asian countries. (China, Hong Kong, Japan, Korea, Taiwan) (N=2141).

Results: Total exposure was 953, 1072, and 1033 patient-years in the placebo, EMPA 10 mg, and 25 mg groups, respectively. The incidence of any AEs, serious AEs, and AEs leading to discontinuation was no higher in patients who were treated with either dose of EMPA than in those treated with placebo. The incidence of hypoglycemia differed according to glycemic-lowering medications used at baseline. Events consistent with urinary tract infection occurred less frequently with EMPA than placebo (5.3-5.8 vs. 7.2/100 patient-years). Events consistent with genital infection occurred more frequently with EMPA than placebo (1.5-1.7 vs. 0.2/100 patient-years). The incidence of AEs consistent with volume depletion was similar across treatment groups (0.8-1.4/100 patient-years). Rates of bone fractures, renal AEs, venous thromboembolic events, hepatic injury, lower limb amputation and diabetic ketoacidosis were similar or no higher with EMPA vs. placebo.

Conclusions: In this pooled analysis, EMPA was well tolerated in the East Asian patients with T2DM based on >3000 patient-years’ exposure, consistent with results from the overall analysis population. The result was in line with package inserts in East Asian countries and did not raise new safety concerns.
and glucose intolerance, and evaluated the therapeutic potential of Tofogliflozin and Pemafibrate combination therapy on NASH development. Male C57BL/6J mice were injected multiple low dose STZ (40 mg/kg) for 5 days and fed high-fat diet (HFD). These mice showed hyperglycemia and higher body weight gain, and glucose intolerance compared with wild type mice. In addition, novel NASH/HCC model shows sequential histological changes from fatty liver to NASH (20 weeks), and all mice developed hepatocellular carcinoma after 52-week HFD feeding. Using our NASH/HCC model, we conducted the prevention study of Tofogliflozin and Pemafibrate (mono-therapy or combination therapy) against NASH development. The combination therapy has significantly prevented body weight gain from 3 weeks after treatment and this effect was persisted throughout study. While Tofogliflozin or Pemafibrate treatment markedly decreased blood glucose and triglyceride levels, the combination therapy showed the synergistic effect compared to mono-therapy groups. Histological analysis revealed Tofogliflozin or combination therapy group markedly suppressed ER-TR7 (fibroblast) and ballooning degeneration. Furthermore, these treatment groups significantly improved NAS score (NASH activity score). These results suggested that Tofogliflozin/Pemafibrate combination therapy would be a beneficial for NASH/NASH treatment.

Supported By: Kowa Company, Ltd.

1154-P
Influence of SGLT2 Inhibitor on Resting Heart Rate (RHR) and Factors Related to Its Changes
YASUHITO MATSUBAYASHI, TOSHIKAI NOJIMA, AKIHITO YOSHIDA, HIDEKI SUGANAMI, TAKAHIRO YAMADA, KAZUYA FUJIHARA, SHIRO TANAKA, KOHEI KAKU, HIROHITO SONE, Niigata, Japan; Tokyo, Japan; Kyoto, Japan; Kurashiki, Japan

An elevated resting heart rate (RHR) is a risk factor for vascular complications in patients with and without type 2 diabetes mellitus (T2DM). Recently, the beneficial effects of SGLT2 inhibitors (SGLT2i) on cardiovascular and renal events were reported in large-scale clinical trials. However, their mechanisms are not fully clarified. This study aimed to investigate the effect of SGLT2i on RHR and the clinical factors that affect changes in RHR in patients with T2DM. Analyzed were 419 T2DM patients on diet and exercise therapy who received an SGLT2i, tofogliflozin (TOFO), or a placebo as initial monotherapy in two TOFO phase 2 and 3 studies. Adipose tissue insulin resistance (Adipo-IR) was calculated by the product of fasting free fatty acid and fasting insulin. Differences in heart rate-related variables between TOFO and the placebo were analyzed with an ANCOVA model. Multivariate analysis was performed to clarify independent factors that were associated with changes in RHR. Baseline characteristics were: male (67%), age (mean: 58 years), Hba1c (8.1%), BMI (26 kg/m2), RHR (66 bpm), eGFR (84 mL/min/1.73m2) and adiponectin (32.5 pmol/L). Concerning the effects on RHR, TOFO reduced RHR levels (least squares mean: -1.7 and -1.1 bpm, p<0.01 vs. baseline, p<0.05 vs. placebo) at weeks 12 and 24, respectively. Changes in RHR were significant from baseline to 24 weeks were 7.7, 0.7, -.37, and -1.2, respectively. The change in RHR at week 24 did not correlate with changes in Hba1c, body weight and systolic blood pressure; however, it was correlated with baseline RHR levels (r = -0.37) and the change in Adipo-IR (r = 0.39) significantly. Multivariate analysis indicated that higher RHRs and Adipo-IR levels at baseline were independently associated with a greater reduction in RHR. Our results showed that the beneficial effects of the SGLT2i on cardiovascular and renal events may be associated with suppression of the sympathetic nervous system by improvement in Adipo-IR and amelioration of hyperinsulinemia.

1155-P
The Novel Use of Nanotechnology Structured Water Magnalifie to Control Blood Glucose Level in Type 2 Diabetic Patients
ALI K.M. SAMI, KAWA H. AMIN, MOHAMED E. KURMANJI, Sulaymany, Iraq

Introduction: Nanotechnology structured water is a new type of water that is produced using special modulators to change and add new properties to water molecules. Objectives: To find out the effect of drinking nanotechnology structured water on blood glucose levels in patients with type 2 diabetes mellitus. Patients and Methods: Type 2 diabetes mellitus patients (n=387) with only oral hypoglycemic drugs were blindly divided into 2 groups. Group A (191 patients) supplied with nanotechnology structured water and group B (196 patients) supplied with ordinary bottled water. Water bottles were unla- beled and patients were unaware of the type of water given to them. Blood glucose level was measured as Glycated Hemoglobin (HbA1c) in the same laboratory. Tests were done before starting drinking the water given to the patients and then every week thereafter for 8 weeks. Results: Significant decrease in HbA1c of -0.44% was observed in group A compared to group B of 0.01%. Conclusion: Nanotechnology structured water may be considered as a potential effective supplement to oral hypoglycemic agents.
patients as baseline then measured at the end of the third month of drinking the given water in a daily dose of (500 ml /25 kg of body weight).

Results: At the end of the the study, only 352 patients were followed (35 patients dropped out for different reasons). Group A (n=183) (aged 24 to 76, mean 50.2) years with male to female (56.3%: 43.7%), and group B (n=199) (aged 30 to 777, mean49.3) years with male to female (41.1%:58.9%). Group A showed significant difference between baseline HbA1c 8.1%±1.36 vs. HbA1c after 3 months 6.6%±0.85 (p<0.001). While group B showed no significant difference in pre-post HbA1c tests 7.9%+/-1.36 vs. 7.8% +/-1/16 (p=0.274). The percentage of Patients with HbA1c<7 in Group A increased from (25.1%) at baseline to (61.2%) after 3 months, while in group B, the percentage of patients with HbA1c <7 decreased from (27.2%) to (19.5%).

Conclusion: Nanotechnology structured water magnifies offers a new way to achieve better control of blood sugar in type 2 diabetic patients. However, further studies are needed to study the long term use of nano-water for the possibility to gradually decrease the needled doses of hypoglycemic agents or to stop them.

**1156-P**

**Initial Beta-Hydroxybutyrate Elevation in Relation to Subsequent Weight Loss in Type 2 Diabetes via the SGLT2 Inhibitor Tofogliflozin**

YUICHI SATO, KYOHIDE NUNO, KOHEI KAKKI, AKIHITO YOSHIDA, HIBEKI SUGANAMI, KUNIKA, JUNNA, KURASHIKI, Japan, Tokyo, Japan

The elevation of ketones is clinically concerned in the use of SGLT2 inhibitor (SGLT2i), however little is known about the association between that elevation and subsequent clinical process. We aimed to clarify the association of the initial beta-hydroxybutyrate (BHB) elevation via the SGLT2i, tofogliflozin with subsequent weight loss in type 2 diabetes patients. Analyzed were 784 type 2 diabetes patients who received tofogliflozin in two phase 3 studies. The participants were divided into four groups according to the quartiles for their change in BHB after 4 weeks of tofogliflozin therapy. The adjusted assessments of variables were analyzed using an analysis of covariance model with the quartiles, their baseline values, age, sex, and eGFR as covariates. BHB levels significantly increased (mean: +107.1 µmol/L) from baseline to week 4. Those changes in the first (Q1), second (Q2), third (Q3), and fourth (Q4) quartiles, respectively, were -33.7, +31.4, +98.0, and +331.1 µmol/L. Glycemic control at baseline was poorer, while CPI was lower within the higher quartiles. The difference of BHB changes among the quartiles was maintained during tofogliflozin therapy. At week 52, the increase of BHB levels from baseline was significant ( +142.7 µmol/L) in Q4, but not changed in Q1. The weight loss at week 52 in Q4 (least square mean: -3.6 kg) was greater than in Q1 (-2.4 kg) although the improvement of hyperglycemia was identical. Furthermore, the reduction in waist circumference and increase in adiponectin were greater in Q4. And the increase in fasting glycemia was identical. Furthermore, the reduction in waist circumference and increase in adiponectin were greater in Q4. The distinct response of BHB elevation was observed early after the SGLT2i, tofogliflozin therapy. The higher initial BHB elevation resulted in the greater reduction in body weight, especially fat mass via lipolysis. The progressive weight loss might be clinically associated with one of the signs of the higher ketone elevation.

**1157-P**

**SGLT2 Inhibitors Increase Bone Strength by Increasing Procollagen Type 1 Amino-Terminal Propeptide in Patients with Type 2 Diabetes**

MASATAKA KUSUNOKI, YUKIE NATSUIME, TETSURO MIYATA, YOSHIHARU OSHIDA, Nagoya, Japan, Tokyo, Japan

With regard to osteoporosis in diabetic patients due to SGLT2 inhibitors (SGLT2is), there is no consensus on its onset as yet. At the meeting of the European Association for the Study of Diabetes in 2015, we reported improvement of bone strength after 6-month treatment with three SGLT2is as revealed by quantitative ultrasound analysis of 115 Japanese type 2 diabetic patients. In this study, we investigated the influence of SGLT2is on the bone strength, density and quality in Japanese patients with type 2 diabetes by the treatment with SGLT2i. In other words, the improvement of the bone strength revealed by ultrasound analysis appears to reflect improved bone quality rather than improved bone density. The serum level of TRACP-5b (a marker of bone destruction) did not differ significantly between before and after treatment, while the serum level of total procollagen type 1 amino-terminal propeptide (P1NP) increased significantly after the treatment (from 35.2 ± 10.3 µg/L to 39.0 ± 12.8 µg/L, P<0.05). The improvement of the bone quality and elevation of bone strength following treatment with SGLT2i appears to be correlated with elevation of the serum P1NP level.

Supported By: Taiso Toyama Pharmaceutical Co., Ltd.
1159-P
Systematic Literature Review and Network Meta-analysis (NMA) of SGLT2i as Monotherapy for Type 2 Diabetes Mellitus (T2DM)
GLENN M. DAVIES, ANN MARIE MCNEILL, ELIZA KRUGER, STACEY L. KOWAL, FLAVIA EJZYKOWICZ, HAKIMA HANNACHI, NILO B. CATER, EUAN MCLEOD, North Wales, PA, San Francisco, CA, Shelby Township, MI, Kenilworth, NJ, New York, NY, Tadworth, United Kingdom

Objective: Indirectly compare the efficacy and safety of ertugliflozin (ertu) from the VERTIS MENDO trial to other SGLT2i when used as monotherapy.

Methods: Pubmed, EMBASE and Cochrane were searched through to end of 2016 for RCTs of 24-26-week duration in T2DM patients with uncontrolled A1C on no antihyperglycemic comparator. Therapists to ertu 5mg and 15mg were low and high doses of SGLT2i licensed in Europe and USA: canagliflozin (can), dapagliflozin (dapa) and empagliflozin (empa). Included outcomes vs. placebo at 24-26 weeks were change in A1C, weight loss (WL), systolic (SBP). A1C >7%, urinary and genital mycotic infections, hypoglycemia and patients with ≥1 adverse event (AE). Evidence was synthesized using both fixed effect (FE) and random effects (RE) Bayesian NMA, with model selection informed by guidelines. Credible intervals (CrI), analogous to 95% confidence intervals, were used to determine significance.

Results: The NMA included 10 RCTs with FE models selected for all analyses except A1C >7% and WL. For change in A1C ertu 15mg was significantly more effective vs. dapa 10mg (mean difference (MD): -0.36%, Crl -0.65, -0.08) and emp 25mg (MD: -0.31%, Crl -0.58, -0.04). There were no other significant differences for efficacy outcomes between ertu and other SGLT2i, except a larger reduction in SBP for cana 300mg vs. ertu 15mg (MD: 3.45 mmHg, Crl 0.15, 6.76). Analyses of safety outcomes did not identify any significant differences or could not be interpreted due to scarcity of events in placebo arms preventing network convergence. The impact of inter-trial heterogeneity was tested, but remains a potential confounder.

Conclusions: In an indirect comparison ertu 5mg was comparable to other low dose SGLT2i at reducing A1C whereas ertu 15mg was more effective vs. dapa 10mg and emp 25mg. With the exception of SBP for ertu 15mg vs. cana 300mg, remaining outcomes were comparable to other SGLT2i for both ertu 5mg and 15mg.

1160-P
SGLT2i Dual Therapy with Metformin (Met) for Type 2 Diabetes Mellitus (T2DM)—Systematic Literature Review and Network Meta-analysis (NMA)
ANN MARIE MCNEILL, GLENN M. DAVIES, ELIZA KRUGER, TIMOTHY REASON, FLAVIA EJZYKOWICZ, HAKIMA HANNACHI, NILO B. CATER, EUAN MCLEOD, North Wales, PA, San Francisco, CA, London, United Kingdom; Kenilworth, NJ, New York, NY, Tadworth, United Kingdom

Objective: Indirectly compare the efficacy and safety of ertugliflozin (ertu) from the VERTIS MET+FATORIAL trials to other SGLT2i as an add-on to MET.

Methods: Pubmed, EMBASE and Cochrane databases were searched through to end of 2016 for RCTs of 24-26 weeks duration in T2DM patients with uncontrolled A1C on MET. Comparator to ertu 5mg and 15mg were low and high doses of SGLT2i licensed in Europe and USA: canagliflozin (can), dapagliflozin (dapa) and empagliflozin (empa). Included outcomes vs. placebo at 24-26 weeks were change in A1C, weight, systolic blood pressure (SBP), A1C >7% and safety outcomes (urinary tract infections, genital mycotic infections, hypoglycemia and patients with ≥1 adverse event (AE). Evidence synthesis used both fixed effect (FE) and random effects (RE) Bayesian NMA, with model selection informed by guidelines. Credible intervals (CrI), analogous to 95% confidence intervals, were used to determine significance.

Results: The NMA included 7 RCTs. ertu was significantly more effective vs. dapa 10mg and emp 25mg. With the exception of SBP for ertu 15mg vs. dapa 10mg and emp 25mg. With the exception of SBP for ertu 15mg vs. other significant differences for efficacy outcomes between ertu and other SGLT2i, except a larger reduction in SBP for cana 300mg vs. ertu 15mg (MD: 3.45 mmHg, Crl 0.15, 6.76). Analyses of safety outcomes did not identify any significant differences or could not be interpreted due to scarcity of events in placebo arms preventing network convergence. The impact of inter-trial heterogeneity was tested, but remains a potential confounder.

Conclusions: Amongst patients requiring triple therapy with SGLT2i added to MET+DPP-4i there was considerable heterogeneity between studies and assumptions of equivalence of background DPP-4i were required. Nonetheless, this analysis indicated that ertu was more effective than dapagliflozin as add-on to MET+DAP and was comparable to other SGLT2i+DPP-4i regimens.

1161-P
Type 2 Diabetes Mellitus (T2DM) Patients with Inadequate A1C Control on Metformin (MET) + DPP-4i—A Network Meta-analysis (NMA) of the Efficacy and Safety of SGLT2i, GLP-1 Analogs, and Insulin
ANN MARIE MCNEILL, GLENN M. DAVIES, ELIZA KRUGER, STACEY L. KOWAL, FLAVIA EJZYKOWICZ, HAKIMA HANNACHI, NILO B. CATER, EUAN MCLEOD, North Wales, PA, San Francisco, CA, Shelby Township, MI, Kenilworth, NJ, New York, NY, Tadworth, United Kingdom

Objective: Indirectly compare the efficacy and safety of ertugliflozin (ERTU) from the VERTIS SITA2 trial to other treatments in patients with inadequate A1C control on MET+DPP-4i.

Methods: Literature was searched up to end of 2016 for RCTs in patients with A1C ≥7% on MET+DPP-4i. Included outcomes vs. placebo at 24-26 weeks were change in A1C, weight, systolic blood pressure, A1C >7%, urinary tract infections, genital mycotic infections, hypoglycemia and patients with ≥1 adverse event. Evidence synthesis used fixed effect and random effects Bayesian NMA, with model selection informed by guidelines. Credible intervals (CrI), analogous to 95% confidence intervals, were used to determine significance.

Results: The NMA included 10 RCTs with FE models selected for all analyses except A1C >7% and WL. For change in A1C ertu 15mg was significantly more effective vs. dapa 10mg (mean difference (MD): -0.36%, Crl -0.65, -0.08) and emp 25mg (MD: -0.31%, Crl -0.58, -0.04). There were no other significant differences for efficacy outcomes between ertu and other SGLT2i, except a larger reduction in SBP for cana 300mg vs. ertu 15mg (MD: 3.45 mmHg, Crl 0.15, 6.76). Analyses of safety outcomes did not identify any significant differences or could not be interpreted due to scarcity of events in placebo arms preventing network convergence. The impact of inter-trial heterogeneity was tested, but remains a potential confounder.

Conclusions: Amongst patients requiring triple therapy with SGLT2i added to MET+DPP-4i there was considerable heterogeneity between studies and assumptions of equivalence of background DPP-4i were required. Nonetheless, this analysis indicated that ertu was more effective than dapagliflozin as add-on to MET+DAP and was comparable to other SGLT2i+DPP-4i regimens.
1163-P
Changes in Energy Balance during Dapagliflozin Therapy in Type 2 Diabetes—The Energize Study
SURYA PANICKER RAJEV, CARL A. ROBERTS, DANIEL J. CUTHBERTSON, VICTORIA S. SPRUNG, EMILY BROWN, JASON C. HALFORD, JR., JOANNE A. HARROLD, GRAHAM J. KEMP, ANDREJ STANCAK, JOHN F. WILDING, Liverpool, United Kingdom

Weight loss during SGLT2i therapy is less than predicted from urinary glucose loss. Modelling suggests a 10-15% compensatory increase in energy intake. We compared effects of 12 weeks’ dapagliflozin 10mg od vs. placebo on food intake in a double-blind, placebo-controlled study with short (1 week) and long-term (12 week) crossover periods. Food intake was measured during test meals at baseline, pre and post each crossover using the Sussex Ingestion Pattern Monitor, continuously recording intake during the meal; primary outcome was the difference after 12 weeks’ treatment. 52 patients with T2DM treated with diet or oral agents were recruited (45 completed; 43% female). Median age 60y, weight 98.4 kg, BMI 34, HbA1c 59.5 mmol/mol. Analysis used a linear mixed model with the random effect as study subject and fixed effects of sex, visit, study arm and arm:visit interaction. Dapagliflozin use was associated with a reduction in HbA1c -9.73 mmol/mol (95% CI 3.91, 16.27; p=0.004), and body weight (-2.84 vs. -0.87 kg) vs. placebo. There was no difference in test meal food intake between dapagliflozin and placebo on food intake 12 weeks median and difference, 2.63g (95% CI, -3.16, 36.9); p=0.659 or at other time points. Dapagliflozin was not associated with a compensatory increase in food intake.

Figure.

1164-P
Effect of SGLT2 Inhibition on Body Water Distribution and Its Relation to Body Composition Measures
HITOMI NAKAYAMA, SHIMEI IWATA, TSUYOSHI OHI, AYAKO NAGAYAMA, KENTARO YAMADA, YUJI TAJIRI, MASATOSHI NOMURA, Kurume, Japan

Many studies have reported the effect of SGLT2 inhibition on body composition. However, its effect on water distribution and the resultant influence on body composition measures are still unclear. The subjects of this study consisted of 29 tofogliflozin (TOFO)-treated type 2 diabetic inpatients aged 48±14 years with BMI of 29.4±6.3 kg/m2, and 29 age- and BMI-matched study consisted of 29 tofogliflozin (TOFO) -treated type 2 diabetic inpatients treated with other therapies. TOFO was administered for 7 days at a dose of 20 mg/day without changing the dose of other drugs. Average glucose levels assessed by CGM decreased from 188±43 to 142±32 mg/dL. Body composition and fluid status were estimated using a multifrequency BIA. The TOFO and the control groups lost 1.64±0.95 and 0.80±0.74 kg body weight, together with 1.31±0.02 and 0.38±0.87 kg body fat, respectively. The reduction of skeletal muscle was not statistically significant due to large variation in either group (0.21±0.84 and 0.39±1.03 kg, respectively). Thus we further analyzed factors associated with the skeletal muscle reduction. Although the change in skeletal muscle mass was correlated with changes in both body fat and body water, a multiple regression analysis showed that the change in intracellular water was the independent factor. Intracellular water was decreased in the TOFO group by 0.29±0.61 kg, but not in the control group. Extracellular water was not changed in either group. Serum sodium concentration was increased in the TOFO group (140.0±1.9 to 141.0±2.7 mEq/L) but not in the control group. The reduction in intracellular water was strongly correlated with that in skeletal muscle in the TOFO group (r=0.863), although there was an inverse correlation in the control group (r=-0.469). These observations indicate that SGLT2 inhibition results in the decrease of intracellular water likely due to increased osmotic diuresis despite plasma glucose reduction. The altered water distribution may affect the assessment of skeletal muscle by BIA.

1165-P
An Observational Study to Evaluate Change in Dose Requirement of Standard Glucose Lowering, Lipid Lowering, and Antihypertensive Therapy Treated with SGLT2 Inhibitor (Canagliflozin) over One Year, in Fifty T2DM Patients
VISHAL GUPTA, VAISHALI TELI, Mumbai, India

Objective: To evaluate effect of Canagliflozin (CA) on dose of other commonly co-administered antidiabetic, antihypertensive (AH) and lipid lowering drugs (AL) over a period of 12 months.

Methodology: Fifty diabetes patients receiving glaucose lowering therapy, AH and AL were treated with CA for a period of 12 months. These patients were followed up at months 3, 6 and 12 for routine metabolic assessment and subsequent amendment in drug therapy. In the present study we evaluated the change in doses of background antidiabetic, AH and AL medication 12 months after CA therapy. Data was represented as Mean ± 2 SD with 95% CI, a p value of 0.05 or lower was considered significant. Paired t test was used to compare average dose of all drug classes at baseline and end of 12 months.

Results: There was a significant reduction in average dose of Gliclazide from 172.5 ± 62.16mg at baseline to 141.25 ± 64.24mg at the end of 12 months (p=0.05) The average dose of metformin reduced from 1.19 ± 0.53g at baseline to 1.05 ± 0.51g at the end of 12 months (p<0.01, not significant NS), Sitagliptin was reduced from 75.78 ± 26.85mg at BS to 75 ± 25.08mg at the end of 12 month (p= 0.91, NS). Basal insulin reduced from 27.14 ± 14.46IU at BS to 25.85 ± 28.63IU at the end of 12 month (p= 0.91, NS) Rosuvastatin slightly increased from 19.16 ± 4.53mg at BS to 19.79 ± 6.35mg at the end of 12 month (p= 0.57, NS) Among AH therapy, average dose of Telmisartan reduced from 43.33 ± 23.94mg at BS to 37.61 ± 22.39mg at the end of 12 month (p=0.42, NS), Valsartan reduced from 103.33 ± 52.45mg at BS to 93.33 ± 54.82mg at the end of 12 month (p=0.65, NS) and Cilnidipine reduced from 15 ± 5.27mg at BS to 17 ± 11.59mg at the end of 12 month (p=0.62, NS).

Conclusion: Canagliflozin was associated with reduced requirements of glaucizide after one year of therapy in type 2 diabetes patients.

1166-P
WITHDRAWN
Changes in Blood Glucose Levels and Body Weight in Patients Administered Sodium-Glucose Cotransporter 2 Inhibitors

HUN-SUNG KIM, EUN YOUNG LEE, KUN-HO YOON, Seoul, Republic of Korea

A few patients who are administered sodium-glucose co-transporter 2 inhibitors (SGLT2i) for the first time often show an increase in their body weight and/or blood glucose levels. In this study, we used an electronic medical record database to identify the factors that affect blood glucose levels and body weight after the administration of SGLT2. We investigated 1,663 patients who had been prescribed SGLT2i for the first time in a Korean hospital (n=1,450) for up to 2 years. Mean age was 57.8 years, 25.8% were 65 years old, or on diuretics, ERTU led to a higher incidence of OD events than non-ERTU. In the PBO pool, the incidence of OD events was 2.9%, 2.4%, and 1.0% and the incidence of VD events was 0.8%, 1.0%, and 1.7% with ERTU 5 mg, 15 mg, and PBO, respectively. There was no increase in the proportion of patients with orthostatic hypotension with ERTU treatment.

ERTU was associated with small, early decreases in eGFR that returned to or towards BL during treatment. Mean decreases in eGFR were larger in patients with BL moderate RI and returned to BL after treatment discontinuation (recently published).

In the broad pool, the incidence of OD events was 2.7%, 2.2%, and 1.4% with ERTU 5 mg, ERTU 15 mg, and non-ERTU, respectively; none were serious and ≤0.2% led to treatment discontinuation. The incidence of VD events was 1.9%, 1.4%, and 1.2% with ERTU 5 mg, ERTU 15 mg and non-ERTU, respectively; 0.2%, 0% and 0%, respectively, were serious and ≤0.1% led to treatment discontinuation.

In patients with moderate renal impairment (RI; eGFR ≤60 mL/min/1.73 m²), the BlA1C tended to demonstrate a marginal rise slightly (from 8.1% to 8.5%, p<0.001). A similar pattern of changes was observed with regard to patients' weight. Significant weight loss and improvement in blood glucose levels were observed in those with a baseline BlA1C level ≥9.0%. However, the weight loss observed was relatively less significant in those with a baseline HbA1c level of 7.0-8.0% and 8.9-9.0%. We conclude that the reduction in blood glucose levels and the weight loss induced by SGLT2i appear to be strongly influenced by associated gender, age, and eGFR. While large-scale clinical studies are needed in the future, it seems worthwhile to check the clinical condition of SGLT2i-prescribed patients in advance and expect changes in weight and blood sugar reduction. Although large-scale clinical studies are needed in the future to conclusively corroborate our results, it is recommended that patients administered SGLT2 be monitored closely for weight changes and improvements in blood sugar levels.

Assessment of Adverse Renal Effects in Patients with Type 2 Diabetes Mellitus (T2DM) Receiving Erugliflozin

SHRITA M. PATEL, MARY A. HICKMAN, ROBERT FREDERICH, BRETT LAURING, STEVEN TERRA, SUSAN L. JOHNSON, SUSAN HUYCK, JAMES P. MANCUSO, North Wales, PA; Grotto, CT; Collegeville, PA; Rahway, NJ, Andover, MA, Durham, NC, Kenilworth, NJ

Erugliflozin (ERTU) is a SGLT2 inhibitor for the treatment of T2DM. Adverse renal effects were assessed in adults with T2DM receiving ERTU relative to placebo (PBO) or active comparators in pooled analyses of 7 randomized, double-blind, Phase 3 trials. Patients (N=4,859) received ERTU 5 mg (n=1,716), ERTU 15 mg (n=1,693), or non-ERTU (PBO; n=1,450) for up to 2 years. Mean age was 57.8 years, 25.8% were ≥65 years old and 51.8% were males. Mean eGFR was 85.3 mL/min/1.73 m² and 9.0% had moderate renal impairment (RI; eGFR ≤60 mL/min/1.73 m²). The mean duration of T2DM was 7.9 years and mean baseline A1C was 8.2%. BL characteristics were similar in the PBO pool.

In the broad pool, the incidence of OD events was 2.7%, 2.2%, and 1.4% with ERTU 5 mg, ERTU 15 mg, and non-ERTU, respectively; none were serious and ≤0.2% led to treatment discontinuation. The incidence of VD events was 1.9%, 1.4%, and 1.2% with ERTU 5 mg, ERTU 15 mg and non-ERTU, respectively; 0.2%, 0% and 0%, respectively, were serious and ≤0.1% led to treatment discontinuation. In patients with moderate renal impairment (RI; eGFR ≤60 mL/min/1.73 m²) or severe and ≥65 years old, or on diuretics, ERTU led to a higher incidence of OD events than non-ERTU. In the PBO pool, the incidence of OD events was 2.9%, 2.4%, and 1.0% and the incidence of VD events was 0.8%, 1.0%, and 1.7% with ERTU 5 mg, 15 mg and PBO, respectively. There was no increase in the proportion of patients with orthostatic hypotension with ERTU treatment.

ERTU was associated with small, early decreases in eGFR that returned to or towards BL during treatment. Mean decreases in eGFR were larger in patients with BL moderate RI and returned to BL after treatment discontinuation (recently published). ERTU is associated with OD, but does not generally lead to VD events or orthostatic hypotension. Consistent with this, observed decreases in eGFR were reversible during treatment or after discontinuation.

Pharmacokinetics (PK) and Pharmacodynamics (PD) of Dapa-gliflozin (DAPA) in Combination with Insulin in Japanese Patients with T1D

HIROTAKA WATADA, MASANARI SHIRAMOTO, SHINYA UEDA, WEIFENG TANG, MICHKO ASANO, FREDRIK A. THOREN, HYOSUNG KIM, TOSHITAKA YAJIMA, HIROTAKA WATADA, MASANARI SHIRAMOTO, SHINYA UEDA, WEIFENG TANG, CLINICAL THERAPEUTICS/NEW TECHNOLOGY—ORAL AGENTS
Modulation of Dapagliflozin-Associated Genital Tract Infections by Saxagliptin—A Pooled Safety Analysis

STEFANO DEL PRATO, EVA K. JOHNSSON, RICARDO GARCIA-SANCHEZ, CLAIRE MORGAN, PETER SARTIPY, RAISA KURLYANDSKAYA, NAYYAR IQBAL, CHANTAL MATHEU, Pisa, Italy; Mithilend, Sweden; Gaithersburg, MD; Warszaw, Poland; Leuven, Belgium.

Incidence of genital tract infections (GTIs), a common adverse event during DAPA 10 mg treatment, may be modified by concomitant DPP-4 inhibitor treatment. We evaluated GTI incidence across randomized trials of dapagliflozin (DAPA) ± saxagliptin (SAXA) as add-on to metformin (MET). Safety data were pooled from seven randomized phase 3 trials; patients with type 2 diabetes (N=3134) receiving DAPA 5/10 mg, SAXA 5 mg or DAPA 5/10 mg + SAXA 5 mg as add-on to MET for 24-52 weeks were included. Data from patients with 52 weeks of follow-up across five of the studies were pooled separately (long-term [LT]-study pool; N=1719). In the 7-study pool, GTI incidence decreased over time with DAPA 5 mg + SAXA 5 mg (1.4%). With LT treatment, GTI incidence decreased over time with DAPA 10 mg + SAXA 5 mg and DAPA 10 mg (month 6, 3.1%; month 12, 1.4%). With LT treatment, GTI incidence decreased over time with DAPA 10 mg + SAXA 5 mg to MET vs. add-on of DAPA 10 mg alone (3.6% vs. 6.6%). The most common events in both groups were vulvovaginal mycotic infections (DAPA + SAXA, 1.5%; DAPA, 2.0%) and balanoposthitis (DAPA + SAXA, 0.9%; DAPA, 1.8%) (Table). This finding was confirmed in the individual studies with the exception of one study comparing GTI incidence with low-dose DAPA 5 mg + SAXA 5 mg (3.1%) vs. DAPA 5 mg (1.4%). With LT treatment, GTI incidence decreased over time with DAPA 10 mg + SAXA 5 mg and DAPA 10 mg (month 6, 3.1% and 5.3%; month 12, 0.9% and 2.1%). In conclusion, add-on of DAPA 10 mg + SAXA 5 mg to MET led to lower GTI incidence than with DAPA 10 mg alone; this effect was maintained after 12 months of treatment.

Table. Incidence of GTIs in the 7-study and LT-study pools.

<table>
<thead>
<tr>
<th>Month</th>
<th>HbA1c (%)</th>
<th>Weight (kg)</th>
<th>HOMA</th>
<th>hsCRP (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAPA 5 mg</td>
<td>DAPA 10 mg</td>
<td>DAPA 5 mg + SAXA 5 mg</td>
<td>DAPA 5 mg + SAXA 5 mg</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>8.6 ± 1.0</td>
<td>8.1 ± 0.7</td>
<td>85.7 ± 14.3</td>
<td>83.3 ± 18.2</td>
</tr>
<tr>
<td>2</td>
<td>7.5 ± 0.9</td>
<td>6.8 ± 0.3</td>
<td>84.5 ± 15.9</td>
<td>82.6 ± 17.4</td>
</tr>
<tr>
<td>4</td>
<td>7.4 ± 0.9</td>
<td>6.5 ± 0.2</td>
<td>84.5 ± 14.5</td>
<td>81.4 ± 17.0</td>
</tr>
<tr>
<td>p&lt;</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.76</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* p value for the change from 0 to 4 months by 1-way repeated ANOVA; +p value for the difference between groups by 2-way repeated ANOVA.

Supported By: AstraZeneca

1171-P

1172-P

A Pilot, Head-to-Head Comparison of Hydroxychloroquine (HCQ) with Pioglitazone (PIO) as Third-Line Agents in Type 2 Diabetic Patients Failing Metformin and a Sulfonylurea (SU)

STANLEY H. HSIA, PETRA DURIAN, MAYER B. DAVIDSON, Los Angeles, CA.

Type 2 diabetes is characterized by insulin resistance and inflammation. HCQ, a commonly used anti-inflammatory drug for rheumatoid arthritis and lupus, is associated with a lower risk of new-onset type 2 diabetes and reports of hypoglycemia in diabetic patients. PIO, an effective 3rd-line agent in patients failing metformin and SUs, has several side effects (e.g., weight gain, fluid retention, fractures) while HCQ has relatively few. We compared 15 patients taking HCQ 400 mg daily with 7 patients taking PIO 45 mg daily, with baseline HbA1c levels of 7.5-11.0% on maximum-tolerated doses of metformin and a SU, in a randomized controlled trial. Glucose control, insulin resistance, and inflammation (highly-sensitive C-reactive protein, hsCRP) were measured at baseline, 2 and 4 months.

Baseline characteristics were not significantly different between groups. Both drugs were well tolerated and significantly improved glucose control; PIO was more effective than HCQ but also caused significantly more weight gain. PIO increased insulin sensitivity while HCQ did not; PIO also significantly decreased hsCRP. HCQ may be beneficial in uncontrolled type 2 diabetic patients as a 3rd-line agent.

Table. Results (Mean ± SD).

<table>
<thead>
<tr>
<th>Month</th>
<th>HbA1c (%)</th>
<th>Weight (kg)</th>
<th>HOMA</th>
<th>hsCRP (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCQ</td>
<td>PIO</td>
<td>HCQ</td>
<td>PIO</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>8.6 ± 1.0</td>
<td>8.1 ± 0.7</td>
<td>85.7 ± 14.3</td>
<td>83.3 ± 18.2</td>
</tr>
<tr>
<td>2</td>
<td>7.5 ± 0.9</td>
<td>6.8 ± 0.3</td>
<td>84.5 ± 15.9</td>
<td>82.6 ± 17.4</td>
</tr>
<tr>
<td>4</td>
<td>7.4 ± 0.9</td>
<td>6.5 ± 0.2</td>
<td>84.5 ± 14.5</td>
<td>81.4 ± 17.0</td>
</tr>
<tr>
<td>p&lt;</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.76</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* p value for the change from 0 to 4 months by 1-way repeated ANOVA; +p value for the difference between groups by 2-way repeated ANOVA.

Supported By: University of California, Los Angeles; Clinical and Translational Science Institute (UL1TR000124), National Institutes of Health/National Institute on Minority Health and Health Disparities (S55MD007598-06)

1173-P

Improvements in Liver Enzymes with Empagliflozin in the EMPA-REG OUTCOME Trial

NAVEED SATTAR, DAVID H. FITCHET, STEFAN HANTEL, JYOTHIS T. GEORGE, BERNARD ZINMAN, Glasgow, United Kingdom; Toronto, ON, Canada; Biberach, Germany; Ingelheim, Germany.

Empagliflozin (EMPA) reduces weight and HbA1c in patients with T2DM, but it is not known if it leads to reductions in elevated liver enzymes reflective of liver fat. We investigated the effect of EMPA on liver transaminases in the EMPA-REG OUTCOME trial.

Patients with T2DM and established CV disease were randomized to receive EMPA 10 mg, EMPA 25 mg, or placebo (PBO) in addition to standard of care. Changes from baseline in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were assessed in all treated patients (N=7020) in the EMPA-REG OUTCOME trial. Patients with T2DM and established CV disease were randomized to receive EMPA 10 mg, EMPA 25 mg, or placebo (PBO) in addition to standard of care. Changes from baseline in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were assessed in all treated patients (N=7020) in the EMPA-REG OUTCOME trial.

In conclusion, EMPA reduced ALT and AST vs. PBO in the EMPA-REG OUTCOME trial.

Patients with T2DM and established CV disease were randomized to receive EMPA 10 mg, EMPA 25 mg, or placebo (PBO) in addition to standard of care. Changes from baseline in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were assessed in all treated patients (N=7020) in the EMPA-REG OUTCOME trial.

In conclusion, EMPA reduced ALT and AST vs. PBO in the EMPA-REG OUTCOME trial.
Dapagliflozin plus Saxagliptin Add-On to Metformin Reduces Liver Fat and Adipose Tissue Volume in Patients with Type 2 Diabetes

JOHN P. WILDING, PAUL HOCKINGS, EVA K. JOHNSSON, JILL MAILASKE, RICARDO GARCIA-SANCHEZ, LARS JOHNSSON, Liverpool, United Kingdom, Malmö, Sweden, Gaithersburg, MD

Oral administration of a fixed-dose combination of the SGLT2 inhibitor dapagliflozin (DAPA) and the DPP-4 inhibitor saxagliptin (SAXA) is approved for improving glycemic control in adult patients with type 2 diabetes (T2D). A 52-week, multicenter, randomized, double-blind, parallel-group trial (NCT02419612) evaluated the efficacy and safety of DAPA 10 mg/d + SAXA 5 mg/d vs. titrated glimepiride (GLIM) 1–6 mg/d in 443 patients with T2D (A1C 7.5-10.5%) on metformin (MET) ≥ 1500 mg/d background. In a substudy, we used magnetic resonance imaging (MRI) to assess effects on liver fat (proton density fat fraction [PDFF]) and visceral and subcutaneous adipose tissue volumes over 52 weeks of treatment. MRI was performed on 59 patients; liver fat and adipose tissue volumes were analyzed for 59 and 57 patients, respectively. There was a significant >30% reduction from baseline in liver fat (P<0.007) and a >10% reduction in adipose tissue volumes (P<0.01) with DAPA + SAXA + MET at week 52 vs. GLIM + MET (Table). In the full study population, DAPA + SAXA + MET decreased body weight and serum levels of alanine aminotransferase and aspartate aminotransferase over 52 weeks.

In conclusion, DAPA + SAXA significantly decreased liver fat and adipose tissue volume vs. GLIM, and reduced serum liver enzyme levels, indicating a favorable metabolic profile of DAPA + SAXA in patients with T2D on MET therapy.

**Table.** Changes in ALT and AST in the EMPA-REG OUTCOME Trial.

<table>
<thead>
<tr>
<th></th>
<th>ALT (U/L)</th>
<th>AST (U/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PBO</td>
<td>EMPA</td>
</tr>
<tr>
<td><strong>Week 28</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-0.73 (0.25)</td>
<td>-2.96 (0.19)</td>
</tr>
<tr>
<td>Difference vs. PBO</td>
<td>-1.26</td>
<td>-0.66</td>
</tr>
<tr>
<td>Tertile 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>1.57 (0.51)</td>
<td>1.51 (0.38)</td>
</tr>
<tr>
<td>Difference vs. PBO</td>
<td>-0.06</td>
<td>-0.16</td>
</tr>
<tr>
<td>Tertile 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>0.29 (0.51)</td>
<td>-1.15 (0.35)</td>
</tr>
<tr>
<td>Difference vs. PBO</td>
<td>-1.45</td>
<td>-0.44</td>
</tr>
<tr>
<td>Tertile 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-3.96 (0.48)</td>
<td>-3.13 (0.34)</td>
</tr>
<tr>
<td>Difference vs. PBO</td>
<td>-4.16</td>
<td>-3.46</td>
</tr>
<tr>
<td><strong>Week 164</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-1.80 (0.36)</td>
<td>-0.51 (0.33)</td>
</tr>
<tr>
<td>Difference vs. PBO</td>
<td>-1.26</td>
<td>-0.66</td>
</tr>
<tr>
<td>Tertile 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>2.46 (0.72)</td>
<td>2.32 (0.49)</td>
</tr>
<tr>
<td>Difference vs. PBO</td>
<td>-0.13</td>
<td>-0.15</td>
</tr>
<tr>
<td>Tertile 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>0.04 (0.71)</td>
<td>-0.06 (0.48)</td>
</tr>
<tr>
<td>Difference vs. PBO</td>
<td>-0.01</td>
<td>-0.08</td>
</tr>
<tr>
<td>Tertile 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-7.33 (0.65)</td>
<td>-4.51 (0.57)</td>
</tr>
<tr>
<td>Difference vs. PBO</td>
<td>-2.22</td>
<td>-2.35</td>
</tr>
</tbody>
</table>

Mixed model repeated measures analysis in patients treated with ≥1 dose of study drug based on observed cases. Changes from baseline are adjusted mean (standard error), Differences vs. PBO are adjusted mean (95% confidence interval). Tertile 3 indicates the highest tertile by baseline value. All patients: N=2333 for PBO; N=4668 for EMPA. *p<0.05; **p<0.01; ***p<0.001.

Dapaagliflozin Exposure Response in Japanese vs. Non-Japanese Patients with Type 1 Diabetes

VICTOR Sokolov, Tatiana Yakovleva, Shinya Ueda, Joanna R. Parkins-Son, Robert C. Penland, David W. Boulton, Weifeng Tang, Moscow, Russian Federation, Osaka, Japan, Malmö, Sweden, Witham, MA, Gaithersburg, MD

Dapagliflozin (DAPA), an SGLT2 inhibitor, reduces blood glucose by increasing urinary glucose excretion (UGE). The pharmacokinetics and pharmacodynamics of DAPA in Japanese and non-Japanese patients (pts) with type 1 diabetes (T1D) have been evaluated in 2 studies Japanese pr: (NCT01498185, n=42, DAPA 5, 10 mg or placebo [PBO] for 14 days; Non-Japanese: NCT02582814, n=70, DAPA, 1, 2.5, 5, 10 mg or PBO for 7 days). A clear dose-response for 24-hour UGE was seen in the non-Japanese study but not in the Japanese study. An exposure-response model was used to characterize the relationship between DAPA exposure and 24-hour UGE using a nonlinear mixed-effect modeling approach, and the effect of patient-level characteristics (baseline and Day 7) on this was investigated. Covariates were identified using a stepwise procedure. Average self-monitored blood glucose (SMBG) at Day 7, Day 7 change from baseline in total insulin dose, and baseline eGFR all had a significant effect on UGE. SMBG was the most influential. When these covariates are included, the model fits the data well for both populations (Figure; for the Japanese study, 1 and 2.5 mg data were simulated using median AUC from non-Japanese pts, for 5 and 10 mg median covariate values were from the Japanese study). The lack of response in UGE in Japanese pts may primarily be caused by high SMBG, which is likely a result of greater insulin dose reductions in the Japanese study.

**Figure.** 24-h UGE on Day 7 following DAPA treatment in Japanese and non-Japanese patients with T1D.

Supported By: AstraZeneca
**Clinical Diabetes/Therapeutics**

**Posters**

**1177-P**

Reduced Postprandial Hepatic Insulin Clearance via the DPP-4 Inhibitor Anagliflozin Contributed to Improvement in Hyperglycemia in Patients with Type 2 Diabetes Mellitus

YASUHIRO MATSUBAYASHI, TAKAHIRO ABE, SAYAKA MURAISHI, AKIHITO YOSHIOKA, KENJI YOSHIKAWA, TAKAHIRU YAMADA, KAZUYA FUJIHARA, SHIRO TANAKA, KOHEI KAKU, HIROCHI SONE, NIGARA, JAPAN, TOKYO, JAPAN, NAGoya, JAPAN, KYoto, JAPAN, KURASHIki, JAPAN

Recent studies suggested that reduced hepatic insulin clearance (HIC) after mixed meal ingestion was associated with amelioration of postprandial hyperglycemia by supplying sufficient insulin throughout the body and that HIC might be regulated by increases in serum incretins. Despite broad use in practice, the effects of DPP-4 on HIC are little known. Thus, we aimed to clarify the effect of a DPP-4i, anagliflozin (ANA), on HIC in type 2 diabetes patients (T2DM). Patients. Analyzed were 977 T2DM patients (72% male, mean age: 58, HbA1c: 8.0%, BMI: 25 kg/m², HOMA: 26.4, HOMA-IR: 2.7) on diet and exercise therapy who received ANA or a placebo as initial mono-therapy and add-on therapy in five phase 2 and 3 randomized controlled trials (ANA: 766, placebo: 271). Postprandial HIC (P-HIC) from the meal tolerance test was calculated as the ratio: C-peptide AUC_{0-120min} to insulin AUC_{0-120min}. Differences in variables between ANA and placebo were analyzed by an ANCOVA model, with the treatment group as a fixed effect and the baseline value as a covariate. Multivariate analysis was done to clarify possible independent factors associated with HbA1c. After taking ANA for 12 weeks, HbA1c was significantly reduced (-0.85%, p<0.01 vs. baseline) and C-peptide AUC_{0-120min} and insulin AUC_{0-120min} were significantly increased (β=0.25 ng/mL and +3.36 μU/mL, p<0.001 vs. baseline). Conversely, in the ANA group, P-HIC levels decreased significantly from baseline (least squares [LS] mean: Δ-0.059 ng/mL, p<0.001). Furthermore, decreased P-HIC by ANA negatively correlated with P-HIC levels at baseline (r=-0.32, p<0.001). Multivariate analysis showed that higher baseline P-HIC levels produced greater reductions in HbA1c. Our results indicated that ANA reduced P-HIC and that the reduction might contribute to improvements in postprandial hyperglycemia. DPP-4i may improve hyperglycemia partially by regulation of the P-HIC.

**1178-P**

The Elevation of Hematocrit after Administration of SGLT2 Inhibitors Does Not Correlate with Plasma Osmolarity in Japanese Subjects with Type 2 Diabetes

YOSHISIHO WADA, YOSHIYUKI HAMAMOTO, YORIHIRO IWASAKI, YOSHINARI NAKATANI, JUN FUJIIKAWA, SADAOHI HONJO, MEKUMI AKAWA-ABE, AKIHITO HAMASAKI, GOSAKA, JAPAN, OSAKAYAMA, JAPAN

It has been reported that hematocrit is elevated after administration of sodium-glucose co-transporter 2 (SGLT2) inhibitors. However, it remains controversial whether this elevation is caused by its diuretic effect. In this study, we aimed to clarify the mechanism of hematocrit elevation by examining the correlation between hematocrit and several parameters reflecting diuretic effects in subjects with type 2 diabetes who were treated with SGLT2 inhibitors. A total of 70 subjects (male: n=45, age: 53±10.1 SD years, BMI: 29.3±4.5 kg/m², HbAlc: 8.8±1.2%) with type 2 diabetes who were newly administered SGLT2 inhibitors from June 2014 to March 2017 were retrospectively identified from our database. Changes in HbAlc, hematocrit, urine specific gravity, uric acid, serum creatinine and plasma osmolarity levels between before and 30, 60, 90 and 120 days after the administration of the drugs were evaluated. Plasma osmolarity was calculated by the formula ([2 x [Na+ mmol/L] + K [mmol/L] + [BUN [mg/dL]/2.8] + [glucose [mg/dL]/18]) x 0.001. HbAlc was significantly decreased (30d: -0.57±0.53%, p<0.005 vs. baseline, 60d: -0.88±1.04%, p<0.002, 90d: -0.65a±1.10%, p<0.001, 120d: -0.79±1.22%, p<0.001). Hematocrit was increased immediately after and remained high over 120 days (1.3±2%: p=0.05, 1.5±3.9%: p=0.44, 2.5±1.2%: p=0.002, 2.1±1.2%: p=0.05). Urine specific gravity was also increased (0.007±0.101 g/mL: p<0.001, 0.003±0.010: p=0.02, 0.004±0.009: p=0.03, 0.007±0.011: p<0.001). However, uric acid (30d: -0.10±0.80mg/dl: p=0.70), serum creatinine (0.04±0.07mg/dl: p=0.32) and plasma osmolarity (0.87±3.44mOsm/l: p=0.31) did not show change. No correlations were observed between changes in hematocrit and serum creatinine, uric acid or plasma osmolarity.

In conclusion, our data indicate that the elevation of hematocrit after the administration of SGLT2 inhibitors is unlikely to be caused by hyper-concentration via diuretic effect.
Efficacy and Safety of Long-Term Administration of Dapagliflozin for Japanese Patients with Type 2 Diabetes Mellitus

MASAHIRO YAMAZAKI, YOSUKE SAIKAI, TAKURO OKAMURA, MICHIAKI FUKUI, Kyoto, Japan

Background: There have been few studies yet on the efficacy and safety of SGLT2 inhibitor in Japanese people at 2 years and later.

Subjects and Methods: The subjects were 112 patients aged 20 years and older who were administered 5 mg/day of dapagliflozin after outpatient treatment with dapagliflozin between April 2014 and December 2015 at this hospital had been judged as useful by the primary physician. Body weight (BW), systolic blood pressure (sBP), HbA1c, liver enzymes, HDL-cholesterol (HDL-C), and uric acid (UA) were measured during hospital visits, and these data available for analysis, 1.0% of daily CGM time = 0.24 hours.

Results: Dapagliflozin was administered over a period of 104 weeks, and a significant decrease in HbA1c, from 8.5±1.4% to 7.6±1.4% (week 0 vs. week 18). Also, a reduction in the amount of fat was suggested to be related to a reduction in HbA1c.

Conclusion: Dapagliflozin can be safely administered over a period of 104 weeks to Japanese patients with type 2 DM, and effects such as lower blood sugar, reduced body weight, and improved metabolism can be expected. Also, a reduction in the amount of fat was suggested to be related to a reduction in HbA1c.
The mean age was 55 years, 43% were females, and the mean HbA1c was 8.5%. Following SGLT2i initiation, each 0.2% HbA1c reduction was associated with a 10% lower risk of treatment intensification (HR [95% CI]: 0.90 [0.86-0.92]). Similarly, each HbA1c reduction of 0.2% was associated with an 8 to 17% increase in the likelihood of achieving the treatment goals (HbA1c<7% HR [95% CI]: 1.17 [1.12-1.21]; HbA1c<8% HR [95% CI]: 1.09 [1.04-1.10]). Each 0.2% HbA1c reduction was also associated with a 15% decreased likelihood of having an HbA1c=8% (HR [95% CI]: 0.85 [0.78-0.88]). 

In this study of T2DM patients, each HbA1c reduction of 0.2% following the initiation of a SGLT2i was associated with a significant positive impact on treatment intensification and HbA1c goal attainment.

Supported By: Janssen Scientific Affairs, LLC.
**Exploring Hepatic Safety of the Dipeptidyl Peptidase-4 (DPP-4) Inhibitor Vildagliptin in a Real-World Setting**

RAHUEL WILLIAMS, WOLFGANG KÖTHN, CARMEN SERBAN, PAVI M. PALDANKUS, RAYMOND SCHLENGER, London, United Kingdom; Basel, Switzerland

Since the introduction of DPP-4 inhibitors, vildagliptin has accumulated extensive efficacy/effectiveness and safety data from various meta-analyses of clinical trials, large randomized controlled trials, non-interventional studies, and post-authorization safety studies. In this non-interventional post-authorization study, we explored if vildagliptin is associated with an increased risk of hepatic events vs. other noninsulin antidiabetic drugs (NAIDs) in a real-world setting. A cohort study was performed in adult T2DM patients with a vildagliptin or NIAD prescription between January 2005 and June 2014 with data from five European electronic healthcare databases from the UK (CPRD), Germany and France (IMS), Denmark (OPED) and Sweden (National Registers). Patients with cancer, HIV/AIDS or insulin prior to the index date (date of first vildagliptin or NIAD prescription in the study period) were excluded. Age- and sex-adjusted incidence rate ratios (aIRRs) were estimated in current vildagliptin vs. current other NIAD users using negative binomial regression. We included 738,054 patients, of which 20,973 received vildagliptin (mean follow-up 1.4 years, 28,330 cumulative vildagliptin patient-years). The database-specific aIRR estimates for serious hepatic events were not suggestive of an increased risk with vildagliptin (range of individual aIRR: 0.29–0.55), with two data sources having an upper limit of the 95% confidence interval (<1). The aIRR for ALT/AST >3-times upper limit of normal (ULN) together with bilirubin >2-times ULN (only assessed in CPRD) was 0.72 (95% CI: 0.42-1.25). In this real-world setting there was no evidence of an increased risk of hepatic toxicity with vildagliptin exposure compared to other NAIDs across five European databases.

**HbA1c, Weight, and Blood Pressure Changes Associated with Early vs. Late Treatment Intensification with Dapagliflozin in U.K. Primary Care Patients with Type 2 Diabetes**

JOHN P. WILDING, UNA RIDGEY, BETINA T. BLAK, STEPHEN T. NOLAN, PETER FENICI, JESUS MEDINA, Liverpool, United Kingdom; Luon, United Kingdom; Cambridge, United Kingdom; Madrid, Spain

Early treatment intensification in patients with type 2 diabetes (T2D) is often required to achieve glycaemic control. Patients with T2D from the UK Clinical Practice Research Datalink, aged ≥18 years, initiating dapagliflozin between Nov 2012 and Aug 2016 and with prior oral T2D therapy (N=3,774) were included in this study. The relationship between early (2nd line) vs. later (3rd line) use of dapagliflozin and changes from baseline in HbA1c (≥10% absolute reduction), weight (kg) (≥5% relative loss) and systolic BP (>2 mmHg absolute reduction) after 6-12 months were assessed with logistic regression models. Early use of dapagliflozin occurred in 25.2% patients (95/3774) vs. later use in 74.8% (2823/3774). Patients with later use were older (mean 60.1 (SD 10.3) vs. 55.7 (SD 10.5) years), more likely to be male (51.6% vs. 55.2%), had T2D for longer (median 8.1 vs. 4.0 years) and had higher CVD prevalence (13.9% vs. 11.2%). Patients with early and later use of dapagliflozin had similar baseline mean HbA1c levels [9.3% (SD 1.5) vs. 9.2% (SD 1.7)] and BP [134.2 (SD 14.2) vs. 135.0 (SD 14.6) mmHg]. Older patients had lower BMI [mean 33.6 (SD 6.3) vs. 36.5 (SD 6.8) kg/m²] than early users. Early dapagliflozin users experienced mean (SE) reductions of 1.6 (0.07%), 3.8 (0.25%) and 3.0 (0.02) mmHg in HbA1c, weight and BP, respectively, vs. 1.0 (0.04%), 4.6 (0.21%) and 3.1 (0.43) mmHg in later users. Compared to later dapagliflozin use, early initiation was associated with a greater likelihood of adjusted HbA1c reduction ≥1% (OR: 1.68, 95% CI: 1.15-2.45). Weight and BP reductions were observed with similar likelihood among early and late users (weight OR: 0.79, 95% CI: 0.54-1.14; BP OR: 0.87, 95% CI: 0.58-1.30).

In conclusion, glycaemic benefits of dapagliflozin were greater in patients receiving it earlier in their treatment pathway. Weight and BP reductions were achieved with similar likelihood among early and later users.

**Effects of SGLT2 Inhibitors on Insulin Secretion and Insulin Resistance—Results from a Cross-Sectional Study**

NAOKO WASEDA, HIROAKI SATOH, CHISA YOSHIDA, FUKI IKEDA, AKIO KANAZAWA, HIROTAKA WATADA, Tokyo, Japan

SGLT2 inhibitors lower blood glucose levels by inhibiting renal glucose reabsorption independently of insulin action. In addition, SGLT2 inhibitors are known to enhance endogenous glucose production by increasing glucagon level, despite lowering fasting glucose. However, the effect of SGLT2 inhibi-
fam at 10 mg/kg stimulated insulin secretion 2.5-times greater (AUC), without causing hypoglycaemia. CPL207-280CA (at 10 µM) subject to off-targets (Safety47™, BiomAP) and selectivity analysis showed no off-target activity, as well as in MIN6 and HepG2 cells it exhibited broader range of non-toxic doses than its comparator. Finally, in hepatobiliary transporters inhibitory assays (carried out in 10 crucial transporters), CPL207-280CA displayed considerable less propensity than fasiglifam, as favourable IC50 values indicate e.g.: human bile salt export pump (Bsep), >100 and 30 µM; multidrug resistance-associated protein 2 (Mrp2), N.D. and 48 µM; organic anion transporting polypeptide (OATP) 1B1, 17.9 and 0.49 µM; organic anion transporting polypeptide (OATP) 1B3, 43 µM and 48 µM; organic anion transporting polypeptide (OATP) 1A2, 118 and 18.6 µM respectively. We conclude that CPL207-280CA is a potent enhancer of GSIS of β-cell T1DM patients with >100 µM doses and >30 µM doses. This compound can be an effective and safe candidate for the T2D treatment. Therefore we propose CPL207-280CA compound as an effective and safe candidate for the T2D treatment. Supported By: National Centre for Research and Development

**1190-P**

**Dose-Response and Exposure-Response (HbA1c) of Dapagliflozin in T1DM Patients**

JOANNAR. PARKINSON, JOHANNA MELIN, MAGNUS ÅSTRAND, BENGT HAMREN, DAVID W. BOULTON, WEIFENG TANG, Gothenburg, Sweden, Gothenburg, MD

Dapagliflozin is an inhibitor of the human renal sodium glucose co-transporter type 2 (SGLT2), which lowers plasma glucose by promoting urinary glucose excretion. Dapagliflozin is approved for the treatment of type 2 diabetes mellitus in adults. The effects of dapagliflozin in type 1 diabetes mellitus (T1DM) has been evaluated in 2 clinical trials: DEPICT 1 and DEPICT 2 (NCT02268214 and NCT02460397). The aim of this analysis was to use pooled data from both studies and assess the dose-response (DR) and exposure-response (ER) relationship for dapagliflozin on HbA1c reduction in T1DM patients. In both studies, T1DM patients underwent double-blind 24-week treatment with either placebo, 5 or 10 mg dapagliflozin doses. -plus adjustable insulin. Mixed-Effect Model Repeated Measures including DR/ER functions was used to describe the longitudinal HbA1c data. The DR and ER models described good convergence from placebo) in T1DM patients well. DR model predicted HbA1c mean (95% CI) reductions at week 24 (placebo-corrected change from baseline) in T1DM patients to: -0.38% [-0.46, -0.30] for 5 mg and 10 mg doses, respectively, which was in good agreement with the actual observations (-0.42% and -0.37% for 5 mg and -0.45% and -0.42% for 10 mg in DEPICT 1 and DEPICT 2 studies, respectively). The estimated ED50 was 1.39mg and AUC50 was predicted to: -0.38% (-0.46, -0.3) and -0.43% (-0.52, -0.35) for 5 mg and 10 mg doses, respectively. Further, the increase in glucose Ox in combination with inhibition of lipid oxidation. The Matsuda Index improved (p<0.01) in DAPA (+0.6±0.20) and DAPA/SAXA (+0.53±0.03) compared to: -0.39% in patients without the pump. The difference in the maximum HbA1c reductions was however only approximately 20% and was not deemed to be clinically relevant. Supported By: AstaZeneeca

**1191-P**

**Relatively Consistent Effects of Canagliflozin (CANA) on Outcomes Regardless of Baseline HbA1c in the CANAgiflozin CardioVascular Assessment Study (CANVAS) Program**

JULIO ROSENSTENG, SANAPATH BANTWAL, JOHN P. WILDING, RICHARD DUMAS, GUILLERMO GONZALEZ-GALVEZ, ALPHEE A. FORCERY, KENNETH W. MAHAFEE, DICK DE ZEEUW, GREGORY FULCHER, DAVID R. MATTHEWS, Dallas, TX; Bangalore, India; Liverpool, United Kingdom; Montreal, QC; Canada; Guadalajara, Mexico; Seattle, WA; Beerse, Belgium; Stanford, CA; Groningen, Netherlands; Sydney, Australia; Oxford, United Kingdom

A prespecified analysis of the CANVAS Program assessed the effects of CANA, a SGLT2 inhibitor, on the risk of cardiovascular (CV) CV, mortality, and renal outcomes in participants with type 2 diabetes mellitus (T2DM) and established CV disease (CVD) or with ≥ 2 CV risk factors by baseline HbA1c. The primary composite outcome of CV death, nonfatal myocardial infarction, or nonfatal stroke was significantly reduced with CANA vs. placebo (PBO) in the total cohort by 14% [HR 0.86, 95% CI, 0.75, 0.97, P = 0.02]. Among CANVAS program participants, 4,411 (43%) had baseline HbA1c ≥ 8% (mean HbA1c 8.9%); prior CVD 67%, age 64 years; BMI 32 kg/m²; and BP 136/77 mmHg). The effects of CANA on CV and renal outcomes were similar overall in participants with baseline HbA1c <8% or ≥8%, but there was evidence of statistical heterogeneity between subgroups for CV death and all-cause mortality, where effects on these adverse outcomes were better in participants with HbA1c ≥ 8% (Figure). In summary, CV and renal outcomes appeared better in CANA-treated participants regardless of HbA1c in this hypothesis-generating subanalysis with a suggestion of greater effects on lowering mortality risk in those with higher HbA1c levels at baseline. Supported By: Jansen Research & Development, LLC.

**1192-P**

**Clinical Parameters, Fuel Oxidation, and Glucose Kinetics in T2D Patients Treated with Dapagliflozin plus Saxagliptin Combination**

YUEJUAN LIN, JOHN M. ADAMS II, RUBERT A. MARTINEZ, ANTONINO DI PINO, USIBEL HUSSEIN, ALI M. ALI, CURTIS L. TRIPPLIT, RALPH A. DEFRONZO, EUGENIO CERRIGIUSMO, San Antonio, TX; Catania, Italy; Bangalore, India; Seattle, WA; Sydney, Australia; Dallas, TX; Gothenburg, Sweden; Stockholm, Sweden; Stockholm, Sweden; Catania, Italy; Bangalore, India; Gothenburg, Sweden; Stockholm, Sweden; Sydney, Australia; Dallas, TX; and Beerse, Belgium

To investigate mechanisms responsible for the clinical and metabolic benefits observed with SGLT2 plus DPP-4 in our randomized 3-day T2D patients (A1c=8.6±0.2%, BMI=33.1±1.9) to receive dapagliflozin 10 mg [DAPA], dapagliflozin/saxagliptin 10/5 mg [DAPA/SAXA] or placebo [PCB]. The Baseline OGTT glucose kinetics [3-H-glucose], indirect calorimetry, HbA1c, FFA, and insulin, and glucagon were repeated after 16 weeks of therapy.

Results: Insulin secretion (Δ[IAA120,130 min] during OGTT increased (p<0.05) in DAPA (+0.6±0.1) and DAPA/SAXA (+0.6±0.1), but not in PCB [-0.4±0.2]. The Matsuda Index improved (p<0.01) in DAPA (+0.2±0.1) but not in PCB (-0.1±0.2). The Disposition Index (IS/IR) increased (p<0.05) in DAPA (Δ0.23±0.03) and DAPA/SAXA (Δ 0.2±0.2), but not in PCB (Δ0.03±0.04). The increase in fasting plasma glucagon in PCB (+47±4) and DAPA (+20±2) was blunted (p<0.05) in combo (-7±4 pg/ml). There were no significant changes in fasting plasma FFA. Conclusion: DAPA/SAXA combination therapy was associated with improved glycemic control vs. DAPA due to the attenuation of the rise in EGP. Further, the increase in glucose Ox in combination with inhibition of lipid Ox and glucagon secretion inhibited ketone production which may reduce the risk of DKA. Addition of SAXA improves insulin secretion and prevents the glucagon elevation induced by DAPA.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PCB</th>
<th>DAPA</th>
<th>DAPA/SAXA</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>+0.16±0.27</td>
<td>-0.58±0.42</td>
<td>-0.77±0.01</td>
<td>*&lt;0.05</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>+0.8±0.12</td>
<td>-1.4±0.1</td>
<td>-1.7±0.2</td>
<td>*&lt;0.01</td>
</tr>
<tr>
<td>FPG (mg/dl)</td>
<td>+25±3</td>
<td>-69±6</td>
<td>-86±8</td>
<td>*&lt;0.01</td>
</tr>
<tr>
<td>Mean Glu (mg/dl)</td>
<td>+41±6</td>
<td>+7±6</td>
<td>-96±7</td>
<td>*&lt;0.01</td>
</tr>
<tr>
<td>Basal EGP (mg/kg/min)</td>
<td>+20±0.04</td>
<td>+19±0.04</td>
<td>-0.06±0.05</td>
<td>**&lt;0.01</td>
</tr>
<tr>
<td>A Lipid Ox (%)</td>
<td>-8±6</td>
<td>+16±3</td>
<td>+10±2</td>
<td>*&lt;0.01 and ***&lt;0.001</td>
</tr>
<tr>
<td>Glucose Ox (%)</td>
<td>+5±4</td>
<td>-31±3</td>
<td>-17±2</td>
<td>*&lt;0.01 and ***&lt;0.001</td>
</tr>
</tbody>
</table>

Δ = DAPA and DAPA/SAXA vs. PCB; *** = DAPA/SAXA vs. DAPA and PCB; ** = DAPA/SAXA vs. DAPA; EGP = Endogenous Glucose Production; Ox = Oxidation.

Supported By: AstraZeneeca

**Clinical Therapeutics/New Technology—Oral Agents**

Support: AstaZeneeca

**Poster Discussion**

**ADA-Supported Research**
1193-P

Consistent Outcomes with Canagliflozin (CANA) in Patients with Type 2 Diabetes across Geographic Regions—Results from the CANagliflozin CardioVascular Assessment Study (CANVAS) Program
CAROL H. WYSHAM, ARAPANDEV BHATACHARYYA, MICHAEL TSOUKAS, ESPRIT-312, PRINCETON, NJ, APRIL, SLEE, WAYNE SHAW, KENNETH W. MANAFFEY, DICK DE ZEEUW, SpokeK WA, Bangalore, India Montreal, QC, Canada, Guadalajara, Mexico, Seattle, WA, Raritan, NJ, Stanford, CA, Groningen, Netherlands

In the global CANVAS Program [n = 10,142], CANA, an SGLT2 inhibitor, demonstrated risk reductions in cardiovascular (CV) and renal outcomes in patients with type 2 diabetes and established CV disease or ≥2 CV risk factors. A pre-specified analysis evaluated outcomes in patients from different geographic regions. Overall, 2,430 (24.0%) were from North America, 1,021 (10.1%) were from Central/South America, 3,609 (35.6%) were from Europe, and 3,082 (30.4%) were from the rest of the world. The primary outcome was comprised of CV death, nonfatal myocardial infarction, or nonfatal stroke; other CV outcomes and renal outcomes were also analyzed. The primary outcome occurred in 2.80, 2.99, 3.07, and 2.69 patients per 100 patient-years (unadjusted) in North America, Central/South America, Europe, and the rest of the world, respectively. The effects of CANA on the primary outcome were consistent between patients from different geographic regions (interaction P = 0.89) and with the total population [HR (95% CI): 0.86 (0.79, 0.95); 0.90 (0.83, 0.98); 0.88 (0.81, 0.95); 0.87 (0.80, 0.95); 0.86 (0.79, 0.93)], Figure). Similar effects between subgroups were observed in the individual components of the primary outcome, all-cause mortality, hospitalization for heart failure, and progression of albuminuria. The risk reduction observed with CANA on CV and renal outcomes was consistent across geographic regions.

Supported By: Janssen Research & Development, LLC.

1195-P

Euglycemic DKA as an Initial Presentation of Immunotherapy-Induced Insulin-Dependent Diabetes
PRIYANKA IYER, SONALI N. THOSANI, HUGO, TX

New onset insulin dependent diabetes (DM) has been reported in cancer patients (pts) receiving immunotherapy (IO). Typically, pts have Grade 3 hyperglycemia (CTCAE) and sometimes DKA. Euglycemic DKA has been reported in pts on empagliflozin. We present a unique case of euglycemic DKA as initial presentation for immunotherapy induced insulin dependent DM. Pt is a 68 year old man without preexisting DM started on nivolumab for metastatic prostate cancer. Following 2 doses of nivolumab, he developed fatigue, weight loss and Grade 2 hyperglycemia for which he was started on metformin, glipizide, and Empa by his outside physician. His BG levels ranged from 130-200 mg/dl on these therapies. Nivolumab treatment was stopped due to significant adverse effects. On return visit to our clinic, approximately 3 months after initial hyperglycemia, pt complained of persistent fatigue, weight loss and a new fruity odor in his breath. Labs revealed BS of 134mg/dl, bicarb of 19 mEq/L (23-30mEq/L), anion gap (AG) of 17mEq/L (4-14mEq/L). Urine ketones were positive and c-peptide level was 0.3mg/mi (0.8-3.85mg/ml) Pt was advised to immediately stop Empa and follow-up with local ER. When he presented to local ER, approximately 4 days later, he was hyperglycemic with glucose 316 mg/dL and labwork consistent with classic DKA. Pt was initiated on basal bolus insulin regimen and had resolution of DKA. IO mediated DM results from immune mediated islet cell destruction leading to rapidly progressive insulin deficiency. When suspected, these pts should be evaluated for beta cell dysfunction and insulin should be used for glycemic control. This case highlights that SGLT2 therapy should be used with caution in patients with hyperglycemia on immunotherapy as it could mask the diagnosis of DKA. In addition, this case shows that patients taken off of immunotherapy may develop delayed glycemic complications and may need long term monitoring.

1196-P

Effects of SGLT2 Inhibitors on Renin-Aldosterone System for One Month and Six Months in Type 2 Diabetes
IICHIRO MORI, TATSUO ISHIKURA, Gifu, Japan

Previous study has shown SGLT2 inhibitors affect tubule-glomerular feedback in murine densa associated with decreased glomerular filtration rate. Thereby, plasma renin activity (PRA) may acutely increase after treatment with SGLT2 inhibitors. However chronic activation of PRA-aldosterone system may introduce deterioration of atherosclerosis and fibrosis of heart muscle. The purpose of this study is to examine alterations of PRA and aldosterone concentration (PAC) after treatment with SGLT2 inhibitor in type 2 diabetic patients (T2D). We measured PRA and PAC in T2D (age 68±18 years old, men: female = 7:2) from 2014 to 2017. Moreover, we could measured each metabolic parameters such as blood glucose, HbA1c, urinary Na/creatinine and blood pressure before and after treatment with SGLT2 inhibitors (SGLT2I) for 1month and 6months in T2D. We analyzed these results with paired t test using JMP12 2.0. SGLT2i significantly increased PRA for 1 month, but not PAC for 1 month and 6 months as follows; before PRA 1.9±2.4 ng/ml/h, 5.8±9.2 ng/ml/h for 1 month (p<0.05) and 2.5±3.1 ng/ml/h for 6months, before PAC 104±65 pg/ml, 105±55 pg/ml for 1 month and 123±82 pg/ml for 6 months, respectively. Moreover, when we examined each metabolic parameter before and after treatment
for 1 month, each body weight, BS, and HbA1c was significantly decreased (p<0.05). SGLT2i increases urinary sodium excretion, which affects macula densa in juxta-glomerular apparatus, and finally stimulates secretion of renin for 1month, but not for 6 months. The alteration of aldosterone were not observed after treatment with SGLT2 inhibitors for 1 and 6 months. These results suggest that SGLT2 inhibitors acutely affects PRA but not PAC, and chronic activation of PRA and PAC, which might cause cardiovascular events are not found.

1197-P The Impact of Metformin Exposure on Lactate Level in Tibetan Type 2 Diabetes Living at High-Altitude Area
YINGYING LUO, YANYAN GENG, QIAN REN, LINGLI ZHOU, XUEMEI LV, SHUYOU MENG, LIHUI YANG, Beijing, China, Usha, China

Objective: To investigate the impact of metformin exposure on lactate level in Tibetan type 2 diabetes living at high-altitude area.

Methods: Our hospital site 3650 meters above sea level. We retrospectively reviewed the in-patients’ documents since Nov 2016 to Dec 2017 in our department. We selected those who did not receive metformin previously and initiated metformin treatment during their stay in the hospital with their lactate level assayed. Firstly, we compared the lactate level before and after metformin treatment. We then did the subgroup analysis according to the patients’ age, baseline lactate level and baseline oxygen saturation degree. Finally, we analyzed the associated factors which may influence the lactate level after metformin exposure by logistic regression test.

Results: There were 132 patients recruited into our study, including 98 male patients. There were no significant difference between the lactate level before and after metformin exposure [3.15±1.82mmol/L vs. 3.29±1.16mmol/L, t=-0.784, P=0.435]. For the subgroup analysis, we found that in the normal lactate level (<2.0mmol/L) and hyperlactatemia group (≥2.0mmol/L) there was a significant elevation of the lactate level after the exposure of metformin. Conversely, a significant decrease of the lactate level was seen in the severe hyperlactatemia group (≥4.0mmol/L) after metformin exposure. There were 73 patients (55.3%) who had an elevated lactate level after the metformin treatment. We also found that baseline lactate level (P=0.001, OR=0.019, 95% CI 0.002-0.159) and baseline oxygen saturation (P=0.04, OR=1.092, 95% CI 1.004-1.187) were two associated factors leading to the elevation of the lactate level after metformin treatment.

Conclusion: Metformin treatment does not lead to the elevation of lactate level in Tibetan type 2 diabetes living at high-altitude area. Metformin can be safely used in high-altitude residents.

Supported By: Shanghai Diabetes Key Laboratory Project (SHKD-KF-1402)

1198-P The Safety of Continuing Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitor during Ramadan Fasting in Muslim Patients with Type 2 Diabetes
YANLI SHAO, YANLI, GWYNETH J. LIM, OON LIAN CHUA, YIP FONG WONG, ESTER YEOH, KIAT MUN SERENA LOW, CHEE FANG SUM, Singapore, Singapore

Methods: This is a single-centre, prospective observational controlled cohort study. Muslim patients aged 18 to 75 years with type 2 diabetes and estimated glomerular rate (eGFR) ≥ 45 ml/min/1.73m2 were eligible if they had no contraindication to observe Ramadan fasting. Patients in study group received stable dose of SGLT2 Inhibitor for ≥ 3 months prior to enrolment and during study period while patients in control group were not on SGLT2 inhibitor and were followed during and after study period. All participants were to attend baseline visit within 2 months before Ramadan and follow-up visit during Ramadan.

Results: A total of 68 patients of similar baseline characteristics were included in the study: 35 in study group and 33 in control group. During Ramadan fasting, patients from study and control group had similar change of body weight (BW) mainly due to fat mass at lower limb and trunk. Reduction of the muscle mass was maintained at lower limbs and trunk but tended to be reduced at arm in ctrl.

Conclusion: Ipragliflozin treatment for 24 weeks resulted in reduction of BW mainly due to lower limb fat and trunk fat. Reduction of the muscle mass at lower limb may be protected by anti-gravity effect.

1199-P Ipragliflozin, a SGLT2 Inhibitor, Reduced Body Weight and Fat Mass but Not Muscle Mass in Type 2 Diabetic Patients Treated with Insulin—A Randomized Clinical Trial
KATSUMARU MORINO, HIDEKO INOUE, KEIKO FUSE, SACHIKO TANAKA, KEIKO KONDO, HISATOMI ARIMA, KATSUKI MIURA, DAIJUSE SATO, NATSUKO CHASHI, SHOSO IDA, ITSUKO MIYAZAWA, OSAMU SEKINE, SATOSHI UGI, HIROSHI MAEGAWA, SUMS-ADDIT-1 STUDY GROUP, Osaka, Japan, Fukuoka, Japan

Objective: Weight gain is a common problem in the insulin treatment. SGLT2 inhibitors are expected to reduce body weight (BW) due to negative energy balance. Previous reports suggested that BW reduction is achieved mainly by loss of body fat, and –20% of reduction is by lean mass. However, the efficacy of SGLT2 inhibitor on BW and body composition remains unclear. We examined in these Japanese T2DM treated with insulin.

Methods: The study was an open label randomized controlled trial. Primary endpoint was the change in BW from baseline to 24 between the two groups. Fifty overweight patients (BMI ≥ 23) who had inadequate glycemic control with insulin treatment were randomly assigned to ipragliflozin (Ipra) or standard treatment (Con) and followed for 24 weeks. Body composition was assessed by DEXA and impedance method.

Results: The change in BW was significantly larger in Ipra compared to Con. Ipra showed significant larger reduction of HbA1c. Total fat mass was reduced in the Ipra compared to Con mainly due to lower limb fat and trunk fat. Total muscle mass was maintained at lower limbs and trunk but tended to be reduced at arm in arm.

Conclusion: Ipragliflozin treatment for 24 weeks resulted in reduction of BW mainly due to fat mass at lower limb and trunk. Reduction of the muscle mass at lower limb may be protected by anti-gravity effect.

Table. Efficacy of ipragliflozin at 24 weeks in Japanese Patients with Inadequately Controlled by Insulin.

<table>
<thead>
<tr>
<th>Ipra (n=23)</th>
<th>Con (n=25)</th>
<th>Mean difference</th>
<th>p value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight kg</td>
<td>74.1±15.0</td>
<td>73.1±13.2</td>
<td>-0.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Fat mass kg</td>
<td>24.1±4.9</td>
<td>23.8±4.9</td>
<td>-0.3</td>
<td>0.435</td>
</tr>
<tr>
<td>Lean body mass kg</td>
<td>45.3±7.5</td>
<td>45.7±7.5</td>
<td>0.4</td>
<td>0.270</td>
</tr>
<tr>
<td>HbA1c %</td>
<td>8.1±0.9</td>
<td>8.3±0.7</td>
<td>0.2</td>
<td>0.065</td>
</tr>
<tr>
<td>Fat mass %</td>
<td>8.9±0.9</td>
<td>11.3±0.9</td>
<td>-2.4</td>
<td>0.045</td>
</tr>
<tr>
<td>Fat mass % lower limb kg</td>
<td>3.7±1.3</td>
<td>3.4±1.6</td>
<td>0.3</td>
<td>0.248</td>
</tr>
<tr>
<td>Fat mass % trunk kg</td>
<td>6.3±1.7</td>
<td>5.9±1.6</td>
<td>0.4</td>
<td>0.023</td>
</tr>
<tr>
<td>Muscle %</td>
<td>2.4±0.9</td>
<td>2.4±0.9</td>
<td>0.0</td>
<td>0.072</td>
</tr>
<tr>
<td>Muscle % lower limb kg</td>
<td>8.3±1.0</td>
<td>8.3±1.0</td>
<td>0.0</td>
<td>0.058</td>
</tr>
<tr>
<td>Muscle % trunk kg</td>
<td>8.5±1.1</td>
<td>8.5±1.1</td>
<td>0.0</td>
<td>0.058</td>
</tr>
<tr>
<td>Z score</td>
<td>0.9±1.1</td>
<td>1.2±1.1</td>
<td>0.3</td>
<td>0.123</td>
</tr>
</tbody>
</table>

Supported By: Astellas Pharma Inc.

1200-P HD-6277, a Selective GPR40 Agonist, Can Improve Beta-Cell Signal-Ing and Insulin Secretion
SEUNG JUN KANG, CHUN HWA KIM, HYO SUN CHOI, G EUNG YANG, SUN HEE LEE, KWAN SDO LIM, MIN AH PARK, DOO YOUNG KIM, JIN YANG, JAE KEOL RHEE, DAEHONG KIM, Yongin, Republic of Korea, Suwon, Republic of Korea

The free fatty acid receptor 1 (FFAR1/GPR40) mediates fatty acid-dependent augmentation of glucose-induced insulin secretion (GIS) in pancreatic β-cells. The objective of the studies described here was to examine the pharmacological properties of HD-6277 in cell based assay and preclinical models of T2D. Insulin secretion was evaluated in INS-1 cells, HD-6277 (0.1–10 μM) treated group enhanced more insulin secretion than sulfonylurea added condition. HD-6277 (100 mg/kg) did not induced hypoglycemia even combinational treatment with metformin (50 mg/kg) in Sprague-Dawley rats. Goto-Kakizaki (GK) rat strains have known as type 2 diabetic model with secondary failure and apoptosis of pancreatic beta-cell. HD-6277 and glimepiride were administered to GK rats of 8 (young) and 26 (old) weeks old, respectively. Glucose tolerance tests (GTT) were performed at the starting and the ending point of the chronic administration. Administration of HD-6277 and glimepiride improved glycemic control and insulin secretion, compared to vehicle control groups in young GK rats, however, chronic administration of glimepiride cause loss of glycemic control efficacy, whereas HD-6277 did not. At the end of chronic administration, glimepiride-treated group demnstrated poor glycemic control and insulin secretion during GTT than HD-6277-treated group. In administration of HD-6277 and glimepiride to old GK

Supported By: Astellas Pharma Inc.

ADA-Supported Research

A322

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—ORAL AGENTS

Supported By: Alexandra Health System of Singapore

Clinical Diabetes/Therapeutics POSTERS

Supported By: Astellas Pharma Inc.
HD-6277, a Novel GPR40 Agonist, Improves Glucose Homeostasis and Enhanced Glucose-Dependent Insulin Secretion in Beta Cells and Type 2 Diabetic Rats

DAMON J. MILLS, CHOI (1), CHUN IWA KIM (1), HYD SUN CHO (1), GOEUN YANG (1), SEIUN JUNG KANG (1), SUN-HEE LEE (1), KWOON SOO LIM (1), MIN AH PARK (1), DOO YOUNG KIM (1), JAE KEOL Rhee (1), Yongin, Republic of Korea

GPR40 is known as free fatty acid receptor 1. Currently, HD-6277, a novel GPR40 agonist, is being developed by Hyundai Pharm in first in human study. The aim of this study was to determine the effects of the novel GPR40 agonist, HD-6277 is a highly potent, selective and orally available small molecule agonist. The potency was measured in vitro and in vivo studies. In vitro potency was determined by HD-6277, TAK-875 and GW9508 (EC50, <10 nM, 27 nM and 14 nM) in stably hGPR40 expressed CHO cells. Selective GPR40 activity of HD-6277 was evaluated by DQOR panel assay. In vivo glucose lowering effect was determined by oral glucose tolerance test (OGTT) and HBa1c in Sprague-Dawley (SD) rats and various type 2 diabetes rats, respectively. Oral administration of HD-6277 (0.1-10 mg/kg) once daily reduced plasma glucose excursion and enhanced insulin secretion in GK, OBO, OLET and ZDF rats. Anti-diabetic efficacy compared with metformin, GLP-1 and DPP-4 inhibitors. HD-6277 enhanced insulin excursion in high glucose condition, whereas in low glucose circumstance was not, thus hypoglycemic risk was low. Repeat dosing for 7day in SD rats, glibenclamide (10 mg/kg) and nateglinide (50 mg/kg) caused hypoglycemia but HD-6277 (100 mg/kg) was not.

In conclusion, HD-6277 shows a promising new drug candidates to treat type 2 diabetes mellitus.

Supported By: Korean Ministry of Health and Welfare (HI42C2710, HI7C2S29)
The Efficacy of Teneligliptin with Metformin in Drug-Naïve Type 2 Subjects

DIPAK B. CHUDASAMA, BANSHI D. SABOQ, DHARMENDRA PANCHAL, FENY PATEL, MAHIRA SAIFYED, DHURUI HASNANI, VIPUL CHAVDA, HARDIK CHANDRA-RANA, RUTUL GOKLANI, Ahmedabad, India

Aim: To assess the efficacy of Teneligliptin with metformin in drug naïve type 2 subjects.

Objective: To assess the efficacy of Teneligliptin with metformin in drug naïve type 2 subjects. Primary outcome observe change in HbA1c, FBS and PPBS from baseline to 48 weeks. Secondary outcome is to note the change in BMI and drug safety.

Method: A retrospective analysis of data from December 2016 till December 2017 was carried out at 4 centers of a chain of Diacare-Diabetes care and Hormone Clinic. The inclusion criteria included newly detected type 2 subjects aged 50-90 years, who were Drug naïve with mean HbA1c 8.0% (7-9%), mean Fasting value 144 mg/dl (+/- 18mg/dl) and mean post meal value 220mg/dl (+/-18mg/dl). All vital parameters with anthropometric data was analyzed, tabulated and reviewed.

Result: N=450 subjects. Reduction in HbA1c after 12 weeks was 1.2% from base line and after 24 weeks it was 1.6% and 1.0% at the end of 48 weeks. 66% of subjects were seen with HbA1c <7% at 24th week. To the rest in whom target was not achieved till 24th weeks, an intervention was added in the form of OHA along with physical exercise and diet.

Drop in BMI at 12 weeks was 0.6 kg/m² to 24 week it was 0.8kg/m² and at 48th week it was 0.5kg/m². 8% of subjects had an AE-intermittent diarrhea and no SAE was detected.

Conclusion: In real scenario, combination of teneligliptin 20mg with metformin 1000mg was associated with clinically significant reduction in HbA1c.

Improved Cardiovascular and Renal Outcomes in the CANAgliBoz Cardiovascular Assessment Study (CANA) Program Irrespective of Baseline (BL) Body Mass Index (BMI)

HAROLD BAYS, LUC VAN GAAL, S.R. ARAVINIO, NAORESH AGGARWAL, RAFAEL VIOLANTE, APRIL SLEE, WAYNE SHAW, KENNETH W. MAHAFFEY, Dick DE ZEEUW, David R. MATTHEWS, Louisvill, KY, Antwerp, Belgium; Banjol, India, Brampton, ON, Canada, Tampico, Mexico, Seattle, WA, Ranjan, NJ, Stanford, CA, Groningen, Netherlands, Oxford, United Kingdom

Obesity and overweight increases the risk of heart and kidney disease. The effects of canagliflozin (CANA) in patients with BL BMI <30 or ≥30 kg/m² was a pre-specified analysis in the CANA program. CANA reduced CV and renal outcomes in patients with T2D and high CV risk (N = 10,142). At BL compared to patients with BMI <30 kg/m², more patients with BMI ≥30 kg/m² had SBP ≥140 or DBP ≥90 mmHg (47.9% vs. 40.3%) and were taking RAAS inhibitors (83.6% vs. 74.6%). Effects of CANA on the primary outcome (CV death, nonfatal myocardial infarction, or nonfatal stroke) and other CV outcomes were consistent between BMI subgroups (Figure). CANA decreased progression of albuminuria in both BMI subgroups with the effect appearing greater in patients with BMI ≥30 kg/m². Further statistical testing did not show a qualitative interaction (Gail-Simons P = 0.675). The comparative benefit of CANA on albuminuria in patients with higher BMI may be due to greater reductions in body weight (placebo-subtracted difference at 1 y: -2.1 and -2.8 kg for BMI <30 and ≥30 kg/m² and BP (SBP: -4.2 and -4.6 mmHg; DBP: -1.0 and -1.7 mmHg for BMI <30 and ≥30 kg/m²; Hba1c reductions were similar with BMI <30 and ≥30 kg/m² ±0.60% and -0.83%. While small statistical heterogeneity may exist, BMI ≥30 vs. ≥30 kg/m² does not appear to be a major determinant of the observed improvements in CV outcomes with CANA.
Methods: In this retrospective study T2DM subjects, who were on fixed doses of Met 1000 to 2000mg and Glin 1 to 6mg daily for 3 months were considered. Subjects with an HbA1c between 8-11% and who were prescribed Teneli 20mg OD for at least 6 months, were shortlisted. Those taking insulin or antidiabetic drugs other than Glin+Met or those whose dose was up-titrated during the study period were excluded. We compared HbA1c, fasting (FPG), postprandial (PPG) plasma glucose, total cholesterol (TC), triglyceride (TG), HDL, LDL, systolic (SBP) and diastolic (DBP) blood pressure at baseline and after 6 months of Teneli initiation.

Results: Data of 562 subjects (229, 41% females), who met the inclusion criteria were extracted for analysis from the hospital records. Mean age of the sample was 52.6% (95% CI: 51.7-53.4) years and duration of diabetes was 7.8 (6.6-8.3) years. Addition of Teneli resulted in a drop in HbA1c from 9.6% (8.2-10.6) to 8.8% (7.1-9.4) (p<0.05). FPG decreased from 158.8 (154.3-163.2) to 127.8 (124.5-131.1) and PPG from 295.4 (290.1-242.0) to 191.0 (185.6-196.0) respectively (p<0.05). Teneli also improved lipid parameters significantly, particularly TC and TG. With Teneli, SBP declined from 136.8 (134.8-137.9) to 129.5 (128.1-130.9) and DBP from 83.1 (82.2-83.9) to 81.0 (80.2-81.9). There was no incidence of severe hypoglycemia, though 18 (3.2%) cases of suspected hypoglycemia were managed at home.

Conclusion: Adding Teneli to Met and Glin combination showed promising role in improving glycemic parameters, lipid components and blood pressure. Low hypoglycemia risk makes the drug a suitable add-on option for those with high HbA1c values.

1209-P

Real-Life Investigation of Effectiveness and Tolerability of Hydroxychloroquine in Type 2 Diabetes Mellitus Patients in India

MANOJ S. CHAWLA, PURVI M. CHAWLA, PAYAL GUPTA, Mumbai, India

Aim: With the increasing incidence of type 2 diabetes mellitus (T2DM) in India (approximately 72 million affected), there is a growing concern and a need for newer, durable and cheaper therapies. Hydroxychloroquine (HClQ), a common anti-malarial also prescribed in rheumatic disease is associated with increased insulin sensitivity and improved glucose tolerance in these patients, with/without diabetes. As a specialty care provider, we initiated an enquiry into the effectiveness and tolerability of HClQ in T2DM patients, uncontrolled on metformin and sulfonylurea (SU), particularly in limited resource countries, with/without diabetes. As a specialty care provider, we initiated an enquiry into the effectiveness and tolerability of HClQ in T2DM patients, uncontrolled on metformin and sulfonylurea (SU) by undertaking this open-label, prospective study at our center.

Methods: A total of 15 T2DM patients, aged between 43-59 years and unresponsive to metformin and SU were included and prescribed an add-on therapy of HClQ at 400 mg once daily for 24 weeks. Change in glycemic and lipid parameters was evaluated at 0, 12 and 24 weeks.

Results: At the end of 24 weeks, there were clinically relevant decreases of 18% and 0.88% in mean fasting plasma glucose and HbA1c, respectively. The total cholesterol, triglycerides, low-density lipoprotein cholesterol and very low-density lipoprotein cholesterol decreased by 13.24%, 19.7%, 13.31% and 26.94% respectively. Teneli also improved lipid parameters significantly, particularly TC and TG. With Teneli, SBP declined from 136.8 (134.8-137.9) to 129.5 (128.1-130.9) and DBP from 83.1 (82.2-83.9) to 81.0 (80.2-81.9). There was no incidence of severe hypoglycemia, though 18 (3.2%) cases of suspected hypoglycemia were managed at home.

Conclusion: Adding Teneli to Met and Glin combination showed promising role in improving glycemic parameters, lipid components and blood pressure. Low hypoglycemia risk makes the drug a suitable add-on option for those with high HbA1c values.

1210-P

Improvements in Blood Pressure (BP) and Markers of Arterial Stiffness with Canagliflozin (CANA) in the CANAGLIFLOZIN Cardiovascular Assessment Study (CANVAS) Program

RAYMOND TOWNSEND, MALA DHARMALINGAM, STEFANO GENOVESE, ANDREW STEELE, JOSE L. ARENAS, SR., APRIL SLEE, ELSA FABBRI, KENNETH W. MAHAFFEY, Philadelphia, PA, Bangalore, India, Milan, Italy, Oshawa, ON, Canada, San Luis, Mexico, Seattle, WA, Rantius, NJ, Stanford, CA

The CANVAS Program demonstrated a reduced risk of cardiovascular (CV) and renal outcomes with the SGLT2 inhibitor CANA vs. placebo (PBO) in adults with T2DM and established CV disease or ≥2 CV risk factors, N = 10,142, mean age, 63.3 ±y, systolic BP (SBP), 136.5 mmHg; diastolic BP (DBP), 77.7 mmHg). This analysis assessed the effects of CANA on BP, pulse, and markers of arterial stiffness including pulse pressure (PP = SBP - DBP) and double product (DP = pulse × SBP). CANA lowered SBP and DBP compared with PBO over the CANVAS Program (mean differences of -3.93 mmHg [95% CI: -4.30, -3.56] and -1.39 mmHg [95% CI: -1.61, -1.17]; both P < 0.001). There were no meaningful differences in pulse over 104 weeks; a ~0.5 bpm reduction in pulse was seen with CANA at Week 26, which remained stable over time, while pulse with PBO was similar to baseline over 104 weeks. CANA also provided reductions in PP and DP compared with PBO (Figure). There was an initial reduction in PP that increased over time with CANA, but remained lower compared with PBO. CANA also provided an initial reduction in DP that was sustained over time. Thus we observed favorable effects of CANA on BP, pulse, and markers of arterial stiffness in patients with T2DM with (un)expected hypoglycemia were managed at home.

Figure. Change in (A) PP and (B) DP with CANA versus PBO over time.

A.  

B.  

Supported By: Janssen Research & Development, LLC.
of these factors may partially explain CV benefits of EMPA in 720M and suggests the possibility of similar benefits in patients with metabolic syndrome without diabetes.

Supported By: Ministry of Health of the Czech Republic (NV000203001)

**1212-P**

**The Effect of Saxagliptin on Adipose Tissue Inflammation in Overweight and Obese Non-diabetic Subjects**

JURAJ KOSKA, TRACY OSREDKAR, KAREN D’SOUZA, SANDEEP SINHA, CHRISTIAN MEYER, PETER REAVEN, Phoenix, AZ

Inflammation plays a crucial role in early stages of both insulin resistance and atherosclerosis development. Preclinical evidence suggests an important role for DPP-4 in the regulation of adipose tissue (AT) inflammation. The present study tests the hypothesis that DPP-4 inhibition by saxagliptin reduces adipose tissue inflammation independent of changes in glucose metabolism. Forty-four overweight or obese individuals without diabetes were randomized to receive once daily saxagliptin (5 mg) or matching placebo (2:1 randomization) for 6 weeks. Adipose tissue biopsies, 4 hour fat-enriched meal challenge tests, and endothelial function measurement were performed at baseline and at the end of each treatment. Forty-two participants completed the study (27 saxagliptin/15 placebo). There were no group differences in the AT expression of inflammation-related genes (MCP-1, CD36, CD68, IL-6, IL-8, TNFp and adiponectin) and protein pathway activation (ERK, JNK and NFKB). Secretion of IL-6 from adipose tissue explants was reduced after saxagliptin compared to placebo (median fold baseline 0.8 saxagliptin vs. 2.3 placebo, p=0.01) and there was also a trend for reduced IL-6 release (0.7 vs. 1.5, p=0.06). After the high-fat meal, plasma glucose was slightly lower after saxagliptin (4 hour AUC, 0.96 vs 1.0, p=0.04) while insulin and triglycerides were similar between the two groups. There were no treatment differences in endothelial function.

In conclusion, reduced AT secretion of IL-6 and IL-8 (trend) in obese non-diabetic subjects suggests saxagliptin may directly reduce AT inflammation. However, this effect was relatively modest, with many other indicators of tissue inflammation remaining unchanged. The reduction in AT inflammation did not appear sufficient to influence postprandial metabolism or endothelial function.

Supported By: AstraZeneca

**1213-P**

**Effect of Metformin on Lymphoid Cancer Cells**

NEEKI AHMADI, SABYASACHI SEN, Washington, DC

Metformin is a commonly prescribed drug for metabolic disorders particularly in type 2 diabetes. In addition to metformin’s established anti-diabetic effect it has a potential for use as an anti-cancer medication, via mitochondrial complex inhibition.

Metformin was employed to determine what effect metformin could have on a common cancer such as lymphoma at a cellular level, we performed a 14 day experiment on the effect of 3 different doses of metformin (0mM, 0.25mM, 0.5mM) on two different lymphoid cell lines, Jurkat and Jeko. Metformin at 0.25mM, is considered physiological. Cells in culture were collected on Days 3, 7, 10, and 14 and RT PCR performed to determine gene expression. We focused on mitochondrial and apoptosis related genes such as cytochrome oxidases (COX2 and 4), nuclear regulatory factor (NRF1), apoptosis gene (P33) and other mitochondrial genes such as PGCA, SOD2, and TFAM.

Results: Jeko cells showed initial significant mitochondrial gene suppression with metformin. The suppression in mRNA gene expression however appear to reverse by day 7. By Day 10 there is a uniform up-regulation in mRNA expressions and the effects stabilized by day 14. Our Jurkat cells showed less consistent mRNA level changes, though the pattern was similar. In summary, Jeko cells, upon initial exposure to metformin, show a decrease in mitochondrial biogenesis and increased apoptosis. This initial suppression seems to be replaced by over-expression of mitochondrial genes over a period of time and its effects stabilize by day 10 of exposure. This phenomenon appears to be shown in both cell lines. We cormbro-rate our expression findings with Sea-Horse respiration study.

Conclusion: We believe that metformin initially causes cancer cell damage, however with time the cells are able to escape that phenomenon by up-regulating mitochondrial genes particularly at physiological doses. In order for metformin to be an effective pro-apoptotic agent in a cancer scenario, brief pulses of supra-physiological doses may be more effective.

Supported By: George Washington University
Cardiometabolic Management—Success of Online CME at Expanding Diabetes Management Past Glycemic Control

AMY LARKIN, MICHAEL LACOUTURE, ANNE LE; New York, NY

We sought to determine if an online continuing medical education (CME) curriculum could improve the clinical knowledge and competence of primary care physicians (PCPs) and diabetologists/endocrinologists (diabs/endos) regarding cardiometabolic management of T2D incorporating recent cardiovascular outcomes trial (CVOT) data.

The online CME activities consisted of a 2 faculty, 15-minute video consultation and an interactive, case-based text activity. A 4-question repeated pairs pre-/post-assessment study design and McNemar’s chi-squared test were used to determine the efficacy of online education. P values < .05 are shown as a measure of significance. The activity launched May 3, 2017, and data collected until July 27, 2017, respectively.

This study demonstrates the success of an online curriculum with multiple educational components consisting of both video discussions and interactive text-based cases improving knowledge and competence of PCPs and diabs/endos. Additional and persistent gaps were identified for future educational targets.

**Table.**

<table>
<thead>
<tr>
<th>PCPs Baseline Knowledge Seen to be Significantly Lower Than That of Diabs/Endos.</th>
<th>PCP Gap (Percent incorrect)</th>
<th>Diab/endo Gap (Percent incorrect)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Avoidance of T2Ds in patient with T2D and HF</strong></td>
<td>36% (N=344)</td>
<td>71% (N=41)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td><strong>Optimizing T2D therapy to meet cardiac-related goals</strong></td>
<td>47% (N=344)</td>
<td>78% (N=41)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td><strong>T2D treatment intensification in patient with CVD</strong></td>
<td>25% (N=344)</td>
<td>54% (N=41)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td><strong>Identification of blood pressure lowering as an extraglycemic effect of SGLT2 inhibitors</strong></td>
<td>49% (N=200)</td>
<td>81% (N=78)</td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>

Significant Overall Improvements were Seen Post Education

<table>
<thead>
<tr>
<th>PCP change Pre-to-post P value</th>
<th>Diab/endo change Pre-to-post P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selection of liraglutide to treat a patient with T2D, CVD, and renal disease</strong></td>
<td>51% (N=344)</td>
</tr>
<tr>
<td><strong>Recognition of T2Ds as a bad therapeutic option in a patient with T2D and HF</strong></td>
<td>27% (N=344)</td>
</tr>
<tr>
<td><strong>Identification of antihyperglycemic agents that have been shown to have positive CV effects</strong></td>
<td>16% (N=200)</td>
</tr>
<tr>
<td><strong>Recognized blood pressure lowering as an extraglycemic effect of SGLT2 inhibitors</strong></td>
<td>13% (N=200)</td>
</tr>
</tbody>
</table>

Supported By: Janssen Pharmaceuticals

**1217-P**

Success of Interactive, Case-Based Education on Improving Physician Clinical Competence

AMY LARKIN, KELLY L. HANLEY, COLLEEN S. HEALY, ANNE LE; New York, NY

We sought to determine if interactive, case-based online continuing medical education (CME) could improve the clinical competence of primary care physicians (PCPs) and diabetologists/endocrinologists (D/Es) regarding clinical application of guidelines and individualized diabetes management. A 3-question case-based and 1-question confidence linked pre-/post-assessment study design and McNemar’s chi-squared test were used. P values are shown as a measure of significance. The activity launched May 3, 2017, and data collected through June 6, 2017. PCPs (N=473) demonstrated a lower baseline knowledge level compared to D/Es (N=198) as shown by the following baseline data:

- 35% of PCPs compared to 61% of D/Es currently individualized treatment for a patient with T2D and HF.
- 22% of PCPs compared to 37% of D/Es correctly individualized treatment for a patient with newly diagnosed T2D and multiple comorbidities.

Significant overall improvements (P < .05) were seen:

- 26% more D/Es and 36% more PCPs correctly individualized the T2D treatment regimen of a patient with comorbid HF.
- 15% more D/Es and 11% more PCPs addressed the importance of lifestyle modification in a patient with newly diagnosed T2D.
- 47% more D/Es and 49% more PCPs correctly individualized pharmacotherapy intensification in a patient with T2D.
- 20% of D/Es and 32% of PCPs reported an increase in confidence initiating or intensifying treatment in patients with T2D.

This study demonstrates the success of interactive, case-based education on improving clinical competence of D/Es and PCPs related to management of T2D. PCPs were found to have lower baseline knowledge and competence compared to D/Es, which is not surprising given the level of specialization in both groups. PCPs may need more foundational education related to guidelines and T2D management than D/Es.

Supported By: Novo Nordisk; Merck & Co., Inc.

**1218-P**

WITHDRAWN
Consistent Accuracy over 10 Days with a Factory-Calibrated Continuous Glucose Monitoring System in Children and Adults

XIAOHE ZHANG, TERRI JOHNSON, DAVID A. PRICE, ANDREW BALO, San Diego, CA

The burden of calibrating continuous glucose monitoring (CGM) systems may be addressed by factory calibration (FC). We evaluated the accuracy of the “G6 FC” CGM System (Dexcom, Inc.) in adults ages 18+ and children ages 6-17 with type 1 diabetes. This was a prospective, non-randomized, multi-center, single-arm study that enrolled 76 subjects at 4 U.S. sites. Subjects participated in either 1 or 2 clinic sessions of varying duration, depending on age. System performance was evaluated in terms of percent accuracy with respect to YSI. Accuracy was characterized as the proportion of CGM values that were within ±15%, ±20% of their paired YSI values for glucose levels >100 mg/dl or within ±15 mg/dl, ±20 mg/dl of YSI for glucose levels ≤100 mg/dl. The two-sided 95% bootstrapped confidence interval (CI) was calculated for its statistical significance. Accuracy was also measured by comparing the difference, absolute difference, relative difference and absolute relative difference of the G6 FC System with respect to YSI.

The G6 FC System showed an overall percent % 20/20 accuracy of 93.9% (95% CI: 89.8, 97.1%) based on 3,532 matched pairs from 62 subjects (25 adults and 37 children). Similarly, the overall percent % 15/15 accuracy was 83.3% (95% CI: 76.7, 89.4%). The Day-1 and Day 10 percent % 20/20 accuracies were 92.2% and 92.5%, respectively; Day-1 and Day 10 mean absolute relative difference (MARD) values were 9.3% and 9.0%, respectively. The percent % 20/20 accuracy was 92.5% for adults and 96.2% for children. The MARD was 9.0% overall, 9.8% for adults, and 7.7% for children. Mean bias and mean relative difference were -8.3 mg/dl and -5.0%, respectively for overall; -10.9 mg/dl and -6.9% for adults; and -4.2 mg/dl and -2.1% for children. The G6 FC System showed high accuracy using multiple metrics for pediatric and adult subjects across days of wear, including Day 1. Elimination of the requirement for calibrations should improve the acceptability and utility of this novel CGM system.
Vit E and PIO combination achieved the primary outcome compared to placebo (65% vs. 22%, p<0.001), but not in the Vit E alone group (36% vs. 22%, p=0.18). The same trend was observed for resolution of NASH, with a significant improvement only in the combination group (57% vs. 18%, p<0.001), but not with Vit E alone (42% vs. 18%, p=0.038). While steatosis grade improved with either combination (p<0.001) or Vit E alone (p=0.018), inflammation (p=0.018) and ballooning (p=0.022) grades only improved with Vit E + PIO. No improvement in fibrosis was observed in any group. Four patients died of cardiovascular causes during the study (2 in Vit E alone and 2 on combination). Weight gain, peripheral edema and hypoglycemia were more frequent in the combination group.

Conclusion: Vit E alone was ineffective to treat NASH in patients with T2DM. While the combination of Vit E and PIO was significantly better than placebo, response rate was similar to that reported for PIO alone in patients with T2DM, suggesting no role of Vit E in this population.

Supported By: U.S. Department of Veterans Affairs

1225-P
Metformin Activates AMPK Signaling but Inhibits Mitophagy in the Mouse Heart

YAWEN ZHANG, MICHAEL M. CHANG, POLINA R. PINKHASOVA, FENGYI ZHAO, TAMAYO KOBAYASHI, YUAN HUANG, SATORU KOBAYASHI, GIANGUANG LIANG, Old Westbury, NY, Brooklyn, NY, New York, NY

Metformin, a commonly prescribed first-line drug for the treatment of type 2 diabetes mellitus, has been shown to reduce cardiac injury under diabetic and other pathological conditions. However, the mechanisms that mediate the cardioprotective effects of metformin remain controversial. One prevailing hypothesis suggests that metformin activates AMPK-autophagy pathway which eliminates protein aggregates and damaged mitochondria, thus protecting the heart from injury. In the present study, we tested this hypothesis using both in vivo and in vitro models. FVB/N mice were administered 200 mg/kg of metformin through gavage once a day for two days. As expected, metformin activated AMPK signaling in the heart as shown by the increased phosphorylation of AMPK alpha at Thr172 and its downstream effector Acetyl-CoA Carboxylase at Ser79. Autophagy and mitophagy were determined by Western blot analysis of LC3-II, a well-established marker of autophagic vesicles. Surprisingly, however, metformin did not affect LC3-II levels in total tissue lysates and significantly reduced LC3-II in mitochondrial fractions, suggesting that metformin actually inhibited rather stimulated mitophagy, contrary to the current belief. This was confirmed by measuring mitophagy flux using lysosomal inhibitors pepstatin A and E64d. The ability of metformin to inhibit mitophagy was also corroborated by a novel dual fluorescent mitophagy reporter showing reduced degradation rate of mitochondria in the lysosomes. All these results show that metformin is able to activate AMPK signaling but paradoxically inhibits mitophagy in the heart, suggesting that the cardioprotective benefit of metformin observed in many different models may be mediated through mechanisms other than autophagy and mitophagy. Future studies will explore the mechanisms by which metformin inhibits mitophagy and protects the heart.

Supported By: National Institutes of Health

1227-P
Combined Treatment with Exendin-4 and Metformin Attenuates Breast Cancer Growth

CHIKAYO IWAYA, TAKASHI NOSIYAMA, TAKAKO KAWANAMI, YURIKO HAMAGUCHI, TOSHIO TAKANO, TOSHINKO YANASE, Fukusuka, Japan

Cancer is a major cause of death in patients with diabetes. Incretin therapy has received much attention, because of its tissue protective effects beyond glycemic control. We have previously reported anti-prostate cancer effect of Ex-4 and metformin (Diabetes 2014, PLOS ONE 2015). In addition, we have recently reported that Ex-4 attenuates breast cancer growth (Endocrinology 2017). Then, we next examined the effect of combined treatment of Ex-4 with metformin in breast cancer cells. In human breast cancer cell lines, MCF-7, MDA-MB-231 and KPL-1 cell, Ex-4 or metformin reduced cell number in a dose-dependent manner. Further, combined treatment of 0.1mM metformin and 10nM Ex-4 significantly attenuated the growth curve progression of breast cancer cells. In BrDU assay, Ex-4 or metformin significantly decreased breast cancer cell proliferation, and further reduction of BrDU incorporation was observed by combined treatment of Ex-4 and metformin, suggesting that Ex-4 and metformin additively decreased DNA synthesis in breast cancer cells. Although apoptotic cells were not observed in Ex-4 and metformin treatment, the increased phosphorylation of AMPK and LC3-II, a novel potent and selective inhibitor of AMPK-9, accelerates healing of diabetic wounds and holds promise as recourse in treatment of DFUs. We report that NF-κB levels correlate with that of active MMP-9, hence it is a useful biomarker in identification of candidates for the treatment option.

Supported By: American Diabetes Association/Pathway to Stop Diabetes (15-CN-06)
Clinical Diabetes/Therapeutics

**Clincial Therapeutics/New Technology—Pharmacologic Treatment of Complications**

1228-P

**Empagliflozin Exhibits Therapeutic Effect in Preclinical Model of Liver Disease (NASH)**

ERIC MAYOUX, THOMAS KLEIN, MICHAEL MARK, Ingeheim, Germany; Biberach, Germany

Nonalcoholic steatohepatitis (NASH) and diabetes are common conditions that coexist and drive adverse outcomes. Empagliflozin (empa), a sodium-glucose co-transporter-2 inhibitor (SGLT2i), has achieved a 38% reduction in the cardiovascular (CV) and all-cause mortality in type 2 diabetes patients with high CV risks. In preclinical models, SGLT2 inhibitors have been reported to increase insulin sensitivity, decrease body weight and reduce markers of oxidative stress and inflammation in tissues. Therefore, we investigated the effect of empal in a mouse model of NASH and hyperglycemia. Neonatal male mice (2 days after birth) were injected subcutaneously with streptozotocin and then were fed with a HFD for 4 weeks of age. Then from 6 to 8 weeks of age, mice were treated by oral gavage with vehicle, empal (10 mg/kg) in comparison to telmisartan (telm, 15 mg/kg) as positive control. A group of mice, under normal diet and without STZ injection were used also as normal controls. NAS, (Histological NAFLD Scoring) evaluating fat deposition, inflammation and ballooning as well as mRNA expression for inflammation markers were performed. Blood glucose level was significantly increased in the vehicle group (525 mg/dL) compared to the normal group (50 mg/dL). Empa significantly decreased the blood glucose (261 mg/dL) while telm did not (429.4 mg/dL). NAS was significantly increased in the vehicle (4.1) compared to the normal control (0.0). Groups and significantly decreased in telm (1.4) and empal (1.4 ± 1.0) groups compared to the vehicle group. Telm but also empal reduced collagen deposition and ameliorated the fat deposition. This was accompanied by a significant reduction of hepatic TNFα mRNA (1.7, 2.8 for telm and empal, respectively compared to vehicle group). These features may qualify empagliflozin for the therapy of NASH and raise interest to evaluate further the potential of the combination of these two approved drugs, with different modes of action in the treatment of liver diseases.

1229-P

**Identification of Glucosepane Cross-Link Breaking Enzymes**

MATTHEW STREETER, TYLER N. GODDARD, JASON M. CRAWFORD, DAVID A. SPIEGEL, New Haven, CT. West Haven, CT

Glucosepane is a member of the class of advanced glycation end-products (AGEs), which form non-enzymatically in the human body. Glucosepane, is the most abundant AGE found in human collagen and has been implicated in the pathophysiology of various conditions ranging from diabetes to normal human aging. Glucosepane crosslinks impact the structural and mechanical properties of collagen and contribute to stiffening of collagenous tissues and vascular dysfunction. We have previously demonstrated the total synthesis of glucosepane, enabling methods for detecting and targeting glucosepane. The present study seeks to identify enzymes that are capable of catalyzing the decomposition of synthetic glucosepane crosslinks. To identify glucosepane crosslink breaking enzymes, we developed a novel screening technology based on metagenomics. Using this strategy, four enzymes were identified for in vitro validation of glucosepane degradation activity. Thus far, our efforts have focused on identifying metabolites of one class L-like enzyme in particular, since it is heterologously expressed at high levels and does not require any unusual cofactors. In vitro enzymatic assays showed that incubation of glucosepane with the class L-like enzyme led to a product consistent with citrulline. We are currently in the process of evaluating the enzyme’s mechanisms of action and identifying other metabolites generated. This is the first demonstration that glucosepane can be broken down enzymatically. Our findings may provide new insight into the role of glucosepane in aging and disease and aid in the development of novel therapeutic strategies for targeting glucosepane.

Supported By: American Diabetes Association/Pathway to Stop Diabetes (1-17-VSN-04 to D.A.S.)

1230-P

**Long-Term Safety and Tolerability of Dasiglucagon, a Stable-in-Solution Glucagon Analog**

JESSICA R. CASTLE, MIKAEL ELANDER, SEAN A. O’HALLORAN, Portland, OR. Glostrup, Denmark; Harrogate, United Kingdom

Several groups are developing fully integrated dual-hormone artificial pancreas systems, which deliver insulin or glucagon in response to changes in glucose to maintain euglycemia. These systems hold the potential to transform management of type 1 diabetes, but in order to be realized these systems require a stable-in-solution glucagon analog suitable for chronic use. Dasiglucagon is a novel glucagon analog stable in liquid formulation. The present studies evaluated safety and tolerability of chronically administered dasiglucagon in rats and dogs.

Rats and dogs were dosed s.c. daily for 26 and 38 weeks, respectively, in 4 groups of 20 rats with 0 (vehicle), 0.5, 2, or 8 mg/kg/day; 4 groups of 4 beagle dogs with 0, 0.02, 0.1, or 0.3 mg/kg/day. Glucose and insulin levels increased in a dose-dependent manner in all treated animals. In dogs, heart rate increased at the 0.1 and 0.3 mg/kg/day dose level. Liver and kidney weights increased at all dose levels for in both species, and microscopic pathology demonstrated increase in hepatocyte glycogen vacuolation and increase in chronic progressive nephropathy (a normal finding in aging rats). Heart weights increased with no histopathological correlate. All findings showed full/partial recovery after 4-week treatment free periods. Some animals developed anti-drug-antibodies but with no apparent effect on pharmacodynamics. The NOAEL (no observed adverse effect level) dose of 2 mg/kg/day in rats and 0.1 mg/kg/day in dogs represents exposure multiples (AUC) of 22 and 2 compared to anticipated human doses of up to 1 mg/day.

Chronic administration of dasiglucagon multiple times above relevant human doses was well tolerated. All findings were consistent with the known pharmacological effects of glucagon. The risk of glucagon accumulation is not considered relevant for humans treated with dasiglucagon to maintain euglycemia. These findings support long-term human testing of dasiglucagon in dual-hormonal artificial pancreas systems.
Adiponectin Attenuates NLRP3 Inflammasome through Modulating AMPK-ROS Pathway
FANG WANG, WENJUN YANG, LINGHAO WANG, YUXING LIU, ZHAOHUI MO, Changsha, China

It has been demonstrated that NLRP3 inflammasome is a key contributor to obesity-related insulin resistance and type 2 diabetes (T2D), which are characterized with chronic, low-grade inflammation. Adiponectin monophosphate-activated protein kinase (AMPK) is a principle intracellular energy sensor, which prevents the production of proinflammatory cytokines and has beneficial effects on the protection against T2D. Compound C, an inhibitor of AMPK, has been demonstrated to be not only an inhibitor of AMPK, but also has some actions independent of AMPK inhibition. We unexpectedly found 25μM compound C considerably inhibited IL-1β and IL-18 secretion when THP-1 cells were stimulated with 100ng/ml LPS plus 0.5μM palmitic acid (PA). In order to address the underlying mechanism, we suggested that compound C affected NLRP3 inflammasome, a multiprotein complex which controls the processing and production of IL-1β and IL-18. Contrary to our expectations, compound C significantly inhibited NLRP3 inflammasome activation (P < 0.05). Additionally, this effect was reproduced in AMPK siRNA transfected THP-1 cells, indicating that compound C exerts this function through an AMPK-independent mechanism. Mechanistically, we found compound C significantly suppresses mitochondria generated reactive oxygen species (ROS), which is required for NLRP3 inflammasome activation.

In conclusion, we demonstrate for the first time that, compound C significantly attenuated NLRP3 inflammasome by modulating AMPK-ROS pathway, as the reason that suppression of AMPK with small interfering RNA (siRNA) abolished adiponectin-mediated inhibition of ROS and NLRP3 inflammasome. In vivo studies with STZ-induced diabetic mice models, we showed that adenosine-mediated overexpression of adiponectin decreased triglycerides and cholesterol in the serum of diabetic mice. Meanwhile, adiponectin decreased CD68 positive macrophages infiltrated in adipose tissue. Furthermore, adiponectin reduced activation of NLRP3 inflammasome in liver and white adipose tissue (WAT) with western blot assay. Taken together, we report a new mechanism that adiponectin alleviates inflammation through modulating AMPK-ROS pathway, which may have therapeutic implications for T2D and the related metabolic diseases.

Supported By: National Natural Science Foundation of China (81400831), Third Xiangya Hospital of Central South University (LY201718)

Glucokinase-MODY Frequently Misdiagnosed and Inappropriately Treated
SEAN BOYD, MARIA M. BYRNE, Dublin, Ireland

Background: GCK-MODY is an autosomal dominant form of diabetes. Heterozygous inactivating mutations in GCK result in mild, persistent asymptomatic hyperglycemia due to a glucose sensing defect. It is reported that GCK-MODY is not associated with significant diabetic complications and that pharmacological therapy does not alter glycemia.

Aim: We aimed to establish the percentage of GCK-MODY patients on pharmacological therapy and its impact on their glycemic control, along with the incidence of diabetic complications.

Methods: 32 patients were identified. Glycemic tolerance was established using an OGTT. Treatment details were recorded. Diabetic complications were identified. Following genetic diagnosis of GCK-MODY pharmacological therapy with metformin was discontinued in 7 of 11 patients.

Results: Treatment at diagnosis included, insulin (4), sulfonylurea (2), DPP-4 (4), metformin only (11), and diet alone (15). Mean HbA1c at MODY diagnosis in all patients was 45.7±4.4 mmol/mol. 7/11 patients discontinued metformin only and had no change in glycemic control HbA1c (46.8±3.5mmol/mol pre vs. 47.9±3.0 mmol/mol post; p=0.38). 40.6% of those screened had background diabetic retinopathy not requiring treatment; 0.3% had cataracts and 0.125% had CAD.

Conclusion: Prior to genetic diagnosis of GCK-MODY, patients were frequently misdiagnosed, with 50% on pharmacological therapy. Discontinuation of metformin resulted in no deterioration of glycemic control indicating that metformin therapy had no impact on the glucose sensing defect. Background diabetic retinopathy was the commonest complication, but did not require treatment.

Supported By: Irish Endocrine Society

The Effect of Lixisenatide and Dapagliflozin in Nonalcoholic Fatty Liver Disease in Patients with Type 2 Diabetes Mellitus Compared with Sitagliptin and Pioglitazone
ANASTASIOS KOUTSOVASILIS, ALEXIOS SOTROPULOS, MARIA RAPPA, DESPINA PAPADAKI, VLASILIS KORDINAS, CHARALAMPO TAMVAKOS, MARIA BOURIKOU, STAVROS BOUSBOULAS, THEODOROS PEPPAS, Athens, Greece

Introduction: Medications currently taken by patients with NAFLD target concomitant metabolic diseases such as hypertension, dyslipidemia and diabetes.

Aim: The aim of the study was to examine the effectiveness of lixisenatide and dapagliflozin in NAFLD patients with type 2 diabetes mellitus (T2DM) compared with sitagliptin and pioglitazone.

Methods: T2DM patients with NAFLD (n=306) were included in the study. Patients were divided in 4 groups according to their treatment with lixisenatide (n=62), dapagliflozin (n=58), pioglitazone (n=67) and sitagliptin (n=92). All patients also received metformin. Mean follow-up period was 76 weeks ± 2 weeks. The evaluation of liver fibrosis depended on calculation of aspartase aminotransferase (AST) to platelet counts ratio (APRI) index. All patients went through an ultrasonography before being included in the study and after the end of the study.

Results: There were no differences between groups in patient age (p=0.256), duration of T2DM (p=0.283), Body Mass Index (BMI) (p=0.337) and HbA1c (p=0.156). There was a greater improvement of APRI index for the lixisenatide group (1.07 (0.46-1.23) vs. 0.74 (0.38-0.90) p=0.001) compared to dapagliflozin (1.12 (0.59-1.22) vs. 0.83 (0.32-1.01) p=0.010) to pioglitazone (1.19 (0.49-1.27) vs. 0.90 (0.41-1.04) p=0.014) and sitagliptin (1.01 (0.39-1.14) vs. 0.99 (0.38-1.15) vs. 0.98 (0.36-1.14) p=0.368). APRI index’s improvement was accompanied by a significant change of fatty liver in ultrasonography. The decrease of body weight in the lixisenatide (p<0.001) and in the dapagliflozin group (p=0.028) was statistically significant.

Conclusions: Administration of lixisenatide and dapagliflozin led not only to good control of T2DM but also improvement of liver inflammation, alteration of liver fibrosis, and reduction of body weight, which are particularly important factors in patients with T2DM.

Supported By: Irish Endocrine Society

ADA-Supported Research ♦ Moderated Poster Discussion
**1236-P**

**FoxO1 Inhibition Potentiates Endothelial Function and Ischemic Angiogenesis in Diabetes via Suppression of ROCK1/Drp1-Mediated Mitochondrial Fission**

LU TIE, YUNDI SHI, DI WANG, Beijing, China

Diabetes-induced endothelial cell (EC) dysfunction and neovascularization impairment constitute vascular complications with limited treatment regimens. Transcription factor FoxO1 is a key angiogenin regulator and plays a pathologic role in progression of diabetes. The present study was designed to determine the involvement of FoxO1 in impaired EC function and post-ischemic neovascularization in diabetes and investigate underlying mechanisms. We found that FoxO1-selective inhibitor AS1842856 improved blood flow recovery and capillary density in ischemic hindlimb, and rescued the delay of wound closure with a concomitant augmentation of mean perfusion rate in diabetic mice. In vitro, treatment with AS1842856 or FoxO1 siRNA abrogated high glucose-induced apoptosis and-ameliorated capillary tube formation in human umbilical vein endothelial cells (HUVECs). FoxO1 inhibition relieved alterations in mitochondrial networks and significantly suppressed the overproduction of mitochondrial reactive oxygen species (mROS) induced by high glucose in ECs. Expression of dynamic-related protein-1 (Drp1) and phosphorylation at Ser616, a protein required for mitochondrial fission, were enhanced by hyperglycemia, which could be neutralized by FoxO1 inhibition. Moreover, the transcription of Rho-associated coiled-coil containing protein kinase 1 (ROCK1), which phosphorylates Drp1 at Ser616, was shown by luciferase assay to be directly regulated by FoxO1. These findings suggested that FoxO1 is critical to preserve mitochondrial function and function in ECs, and FoxO1 may serve as a therapeutic target for microvascular complications of diabetes.

Supported By: National Natural Science Foundation of China (18162496, 81370405, 80970102), Beijing Natural Science Foundation (7172119), Beijing Higher Education Young Elite Teacher Project (YFP00503), Beijing Golden Bridge Seed Capital Project (Z261609)

---

**1237-P**

**Simplified Transition Algorithm from Intravenous to Subcutaneous Insulin in Nondiabetic Cardiac Surgery Patients with Stress Hyperglycemia**

SAUMETH CARDONA, RODOLFO J. GALINDO, KATERINA G. TSEGKA, MARIA A. URRUTIA, PRIYATHAMA VELLANKI, MAYA FAYFMAN, J. SONYA HAW, FRANCISCO J. PASQUEL, LIMIN PENG, GUILLERMO E. UMPIERREZ, WALNUT CREEK, IL

Intravenous (IV) insulin is recommended to treat stress hyperglycemia (SH) in nondiabetic (non-DM) patients after cardiac surgery. Many patients with SH require transition to subcutaneous (SQ) insulin after stopping IV drip in the ICU. We report a simplified protocol for the transition from IV to SQ insulin in cardiac surgery patients with SH. Patients requiring IV insulin ≥2 U/hour were transitioned to SQ basal bolus regimen at 70% of calculated daily insulin requirement. Patients requiring ≤2 U/hour were treated with sliding scale insulin (SSI), if ≥2 episodes of BG >140 mg/dl patients were started on rescue therapy with basal insulin. Among 150 non-DM patients with SH in the ICU, 30 patients (20%) required ≥2 U/hour and were transitioned to SQ basal/bolus at a mean SQ dose of 0.34 U/kg/day for a duration of treatment of 5.5±3.6 days. A total of 120 (80%) patients required ≤2 U/hour and were transitioned to SSI. Of them, the mean blood glucose (BG) was 129.8±16 mg/dl and only 3 (2.5%) patients required a single dose of basal insulin during the hospital stay. There were no differences in LOS or in a composite of complications of diabetes.

Our results indicate that cardiac surgery patients with SH requiring continual IV insulin ≤2 U/hour in the ICU can be safely transitioned to SSI; however, patients requiring >2 U/hour should be transitioned to basal insulin to maintain glycemic targets.

**Table.**

<table>
<thead>
<tr>
<th>Transition</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n(%)</td>
<td>120 (80)</td>
</tr>
<tr>
<td>BMI, Kg/m²</td>
<td>28.8 ± 6.5</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.6 ± 0.4</td>
</tr>
<tr>
<td>ICU</td>
<td>133.9 ± 17</td>
</tr>
<tr>
<td>Total insulin in the ICU, U/day</td>
<td>57.4 ± 89</td>
</tr>
</tbody>
</table>

---

**1238-P**

**The Effect of Metformin and Dapagliflozin on Epicardial Adipose Tissue in Prediabetes and Type 2 Diabetic Patients**

SHAWNEE A. AL-TALABANY, JONATHAN W. WEIR-MCCALL, WALNUT CREEK, CA

Epicardial adipose tissue (EAT) has been proposed as a therapeutic target. The biguanide, metformin, and Sodium-glucose Cotransporter-2 inhibitors have been reported to improve cardiovascular outcomes. We have investigated the effects of both metformin and dapagliflozin, on EAT in patients with prediabetes and type 2 diabetes respectively.

Methods: EAT area measurements were performed blindly on cine 4 chamber views during the end diastolic phase of the cardiac cycle at baseline and at the end of study treatment using CMR scans in patients that participated in two randomized double-blinded placebo controlled trials: 1) MET-REMODEL (ClinicalTrials.gov NCT02226510) (n=68 patients, mean age 65±8 yrs, mean BMI 31.9 ± 3.6 kg/m²) with prediabetes and/or insulin resistance who received either metformin (2g/day) or placebo for 12 months and 2) REFORM (ClinicalTrial.gov NCT02394241) (n=56 patients, mean age 67±7 yrs, mean BMI 32.5±5.3 kg/m²) with chronic heart failure and type 2 diabetics who received either dapagliflozin (10mg/day) or placebo for 12 months respectively.

Results: Metformin treatment in the METREMODEL trial reduced body weight significantly by 4.2kg (p=0.001) but did not reduce EAT area (metformin -0.1 ± 3.8 cm² vs placebo -0.5 ± 2.9 cm² p = 0.7). In the REFORM trial, dapagliflozin reduced body weight significantly by -1.9 kg (p=0.054) with no significant reduction in EAT area (dapagliflozin -1.0 ± 3.6 cm² vs placebo -0.7 ± 3.1 p=0.8).

Conclusion: In prediabetes and type 2 diabetes, we found that metformin and dapagliflozin treatment resulted in significant weight loss but had no significant effect on EAT. Our findings suggest that the reported cardiovascular benefits of these two diabetic therapies are not likely to be mediated by effects on EAT.

---

**1239-P**

**A Phase 3 Comparison of a Novel Liquid Glucagon Autoinjector to Glucagon Emergency Kit for the Treatment of Severe Hypoglycemia**

MARK P. CHRISTIANSEN, MARTIN J. CUMMINGS, STEVEN J. PRESTRELSKI, POUL STRANGE, Walnut Creek, CA, Chicago, IL, Princeton, New Jersey, NJ

Objective: To prevent medical complications and serious sequelae of severe hypoglycemic emergencies, prompt and reliable rescue intervention is critically important. A novel ready-to-use stable liquid glucagon autoinjector (GAI, Xeris Pharmaceuticals) was evaluated for the rescue treatment of severe hypoglycemia.

Research Design and Methods: A randomized, controlled, double-blind, crossover clinical trial was conducted in 80 adults with T1D (mean age 43.6 years) to compare subcutaneous 1 mg doses of GAI vs. Glucagon Emergency Kit (GEK, Eli Lilly) for the treatment of insulin-induced severe hypoglycemia. Efficacy was evaluated as either an increase in plasma glucose ≥20 mg/dl or an increase in plasma glucose ≥20 mg/dl from a baseline glucose ≤50 mg/dl, within 30 min of dosing.

Results: On intent-to-treat basis, efficacy was comparable between the groups (97.4% GAI; 100% GEK, p=NS), and all subjects were rescued from severe hypoglycemia without additional measures. GAI was similar to GEK in terms of glucose Cmax, Tmax, and AUC (90-90 min). The incidence of AE was low in both groups; the most commonly reported AE was nausea (GAI 20.5%, GEK 12.7%, p=NS), followed by vomiting and headache.

Conclusions: These results demonstrate that GAI is an effective, safe, and well tolerated rescue treatment for severe hypoglycemia and is a viable alternative to GEK.
Effectiveness and Safety of Oral Hypoglycemic Agents as Initial Treatment in Comparison to Insulin Injection in Newly Diagnosed Type 2 Diabetes Mellitus

XI CHEN, YUFAN WANG, AIFANG ZHANG, NIAN WANG, NAI LI, Shanghai, China

Objective: To explore the effectiveness and safety of oral hypoglycemic agents (OHA) and insulin (INS) therapy as initial treatment in patients with newly diagnosed type 2 diabetes mellitus (T2DM).

Subjects and Methods: An retrospective cohort study was conducted between December 2015 and June 2017 in diabetic clinic in Shanghai General Hospital. 195 newly diagnosed T2DM were enrolled. 107 subjects received OHA while 88 subjects received insulin therapy of which 39 switched to OHA in 6 months. The general characteristics, HOMA-B and HOMA-IR, the glycoemic control, glucose control rate and hypoglycemia were compared between OHA group and INS group. All of those data were compared between continued insulin group and switch to OHA group.

Results: 1. The baseline A1C levels were higher and HOMA-B was lower in INS group. While the A1C levels was significantly higher and the rates of glycomic control were significantly lower in INS group than in OHA group after 6 months’ treatment. The incidences of hypoglycemia, changes of BMI were similar in both groups. However, Multiple linear regression analysis indicated that baseline A1C was independently associated with glycemic control (R2=0.005). 2. 24.32% patients switched to OHA in INS group in 6 months. This subgroup was younger, had better glycemic control and more male subjects compared with patients who still used insulin. There were no significant differences in terms of A1C, BMI and HOMA-B at baseline, the changes of BMI and rates of hypoglycemia. Binary logistic regression showed that age was significantly associated with continuous usage of insulin. (P=0.005).

Conclusion: Our results demonstrate that baseline A1C was negatively associated with glycemic control and the younger the more possibility to switch from insulin to oral hypoglycemic agents in real word setting. Incidences of hypoglycemia were similar in OHA and INS groups.

Supported By: Shanghai Pujiang Talent Program (15P00332), Shanghai Municipal Education Commission; Guangfeng Clinical Medicine (20152231)

L-Carnitine and Resveratrol Action on Oxidative Response and Differentiation in H9c2 Rat Cardiomyocytes

ILEANA TERRUZZI, PAMELA SENESI, ANNA MONTESEANO, FERNANDA VACANTE, LIVIO LUZI, Milan, Italy

Diabetic heart disease (DHD) results in structural and functional deterioration due to progressive loss of cardiomyocytes and cardiac stem cells, leading to a premature aging of the diabetic heart. The causes of DHD development are not completely clarified, but it is evident that higher oxidative stress of diabetes induces cardiac structural alterations. Recently, the use of stem cells or cardiac progenitors have inspired the most promising therapeutic strategies but these approaches are limited in diabetic patients. Herein we investigate L-Carnitine (LC) and Resveratrol (RSV) actions on oxidative stress and differentiation process in H9c2 rat cardiomyocytes. H9c2, during proliferation or differentiation condition, were treated with LC (0.5 or 5mM) or RSV (0.1 or 25µM). LC significantly enhanced anti-oxidative response by proliferation decrease in favor of H9c2 differentiation, as shown by oxidative stress condition was evaluated treating cells with LC 48h before exposure to H2O2: LC significantly reduced intracellular ROS concentration in a dose-dependent manner. The most commonly reported AEs were: Prevention of cardiac dysfunction by oxidative stress and to stimulate cardiac progenitor differentiation could recognize LC/RSV as valid adjuvant therapies to preserve cardiomyocytes survival and ameliorate heart regeneration.

1241-P

1240-P

Effect of Testosterone Therapy on Renal and Endothelial Functions in Men with Type 2 Diabetes Mellitus

IRINA A. KHRIPUN, ELENA V. BOVA, SERGEY V. VOROBYEV, Rostov on Don, Russian Federation

Recently, the attention of researchers is attracted to the problem of testosterone (T) deficiency in men. Its negative effect on the cardiovascular system has been established, but the data about the effect of T deficiency on the renal function in patients with type 2 diabetes mellitus (T2DM) haven’t been studied yet.

Aim: Evaluate the effect of T therapy on glycemic control, the renal function and the biochemical parameters of endothelial function in men with T2DM having an androgen deficiency.

Materials and Methods: The study included 80 men (mean age 51.5±6.3 years), with T2DM and T deficiency. Patients were randomized into 2 groups: the 1st-40 men receiving transdermal T (Androgel 50 mg/d) during 9 months and the 2nd group - 40 men who were not assigned to T. Patients underwent a clinical examination, analysis of biochemical parameters of carbohydrate metabolism (fasting glycaemia, HbA1c), renal (creatinin, glomerular filtration rate (GFR) and endothelial functions (p-, e-selectins, ICAM-1, VCAM-1). Statistical analysis was performed with Mann-Whitney and Wilcoxon tests using the Statistica 10 software package.

Results: T therapy in men with T2DM, along with a decrease in body weight by 5.0±2.99 kg (p=0.003) and waist circumference by 5.5±1.5 sm, led to an improvement in carbohydrate metabolism - fasting glycaemia by 22.2% and HbA1c by 1% (p=0.00001). At the same time, a statistically significant decrease in the creatinine concentration and an increase in the GFR by 12.5% (p=0.01), as well as a decrease in the levels of endothelial dysfunction markers (ICAM-1 by 56% and p-selectin by 77 times (p=0.01)) were found. No significant changes in the 2nd group were found.

Conclusion: T therapy in men with T2DM and androgen deficiency leads not only to a decrease of visceral obesity and an improvement in carbohydrate metabolism, but also ameliorates the renal and endothelial functions, which could reduce the rate of progression of vascular complications of diabetes.

Supported By: Russian Science Foundation (14-25-00052)
Telmisartan Combination with Amlodipine Inhibits RAGE
SWETHA SRIRAMOJU, KERRY GOETZ, Astley, NY, Bethesda, MD

Diabetic Retinopathy (DR) is the leading cause of blindness in the United States corresponding to 20,000 new diagnoses annually (cite this). Hyperglycemia is a major risk factor of type 2 diabetes and leads to the formation of plasma proteins known as Advanced Glycation End Products (AGES). In the eye, AGES’s bind to the receptor of the Advanced Glycation End Products (RAGE) eventually leading to DR. The following study analyzed drug targets (single drugs and combination of drugs) that are currently marketed for heart disease, diabetes, and hypertension to understand how they interact with RAGE with the goal of identifying compounds that are predicted to inhibit the ligand-receptor interaction. Docking programs, AutoDock Tools and AutoDock Vina, were used to determine the binding affinity and visual orientation of the drug receptor binding. Cholesterol lowering drugs such as Atorvastatin and Fenofibrate were able to bind to RAGE with a high hydrophobicity and great negative affinity (-7.5 and -7.7). In combination, the hypertensive drugs such as Telmisartan (Angiotensin II receptor blocker) and Amlodipine (calcium channel blocker) bind with the RAGE receptor with a high hydrophobicity and high negative affinity (-9.7). Metformin administered alone or in combination was not shown to bind to RAGE. Overall this analysis shows that a combination of hypertensive drugs and cholesterol lowering drugs may decrease the progression of DR in type 2 diabetes.

Health Economics Analysis of Point-of-Care HbA1c Monitoring in Belgium, Germany, and Switzerland.

Erlangen Health Economics Analysis of Point-of-Care HbA1c Monitoring in CERs of other interventions ranged from $30,000 to $4,817,000 per QALY or life year gained (LYG)—cost saving (≤$50,000); marginally cost-effective ($50,000 < ICER < CER ≤ $100,000); cost-effective ($100,000 < ICER < CER ≤ $150,000) with some level of uncertainty; and very cost-effective (CER ≤ $150,000). As a result of our analysis, 848 million (on average, 233 per patient in the cohort) and 118 million (on average, 422 per patient in the cohort) in Switzerland savings amounted to 118 million (on average, 422 per patient in the cohort). The sensitivity analysis showed robustness of our findings.

Conclusions: Our health economics analysis suggests that the POC HbA1c monitoring in patients suffering from DM type 2 may reduce overall healthcare costs in Belgium, Germany, and Switzerland.

Methods: We developed a health economics model comparing the strategy of using point-of-care (POC) HbA1c monitoring with the strategy of using conventional laboratory-diagnostic (LD) in patients suffering from DM type 2. We followed cohorts of patients diagnosed with DM type 2 in Belgium, Germany and Switzerland for the period of 15 years and estimated the costs of complications (amputation, cataract extraction, kidney failure, heart failure, stroke, and microvascular disease or myocardial infarction) using the local data. To assess the validity of the assumptions and robustness of the model, a thorough sensitivity analysis was undertaken.

Results: In patients with DM type 2, POC HbA1c monitoring resulted in savings of $9.2 million in Switzerland and $118 million in Belgium when compared to conventional LD monitoring; corresponding savings in Germany were $848 million (on average, 233 per patient in the cohort) and in Switzerland savings amounted to $118 million (on average, 422 per patient in the cohort). The sensitivity analysis showed robustness of our findings.

Conclusion: Our health economics analysis suggests that the POC HbA1c monitoring in patients suffering from DM type 2 may reduce overall health care costs in Belgium, Germany, and Switzerland.
Cost-Effectiveness of Telephone-Delivered Behavioral Skills Intervention for African-American Adults with Diabetes

LEONARD E. EGDE, CLARA DISMUKE, CHRISTIAN EILER, REBEKAH J. WALKER, Milwaukee, WI, Charleston, SC

Background: To investigate cost differences between intervention arms of a telephone-delivered self-management training for African Americans with diabetes.

Methods: This RCT used a 2x2 factorial design, randomizing African American adults with poorly controlled diabetes to: 1) knowledge only, 2) skills training only, 3) combined knowledge and skills training, or 4) control group receiving general health education. The primary outcome for cost-effectiveness was glycemic control (HbA1c) at 12-months post-randomization. Costs for healthcare utilization were measured using Medical Expenditure Panel Survey (MEPS) estimates and costs for lost wages were estimated using interval regression. All costs were adjusted to 2012 dollars. Cost utility was quality-adjusted life years (QALYs) estimated via the area under the curve technique using utilities obtained from respondents’ answers to SF-12 questions and mortality estimates based on CDC lifetables. Empirical joint distribution of incremental costs, QALYs, and cost effectiveness acceptability curves were generated using non-parametric bootstrapping.

Results: There was no significant difference in cost (p=0.44) or change of QALYs between arms (p=0.38). With no statistically significant difference in cost, the incremental cost-effectiveness ratios (ICER) were not significant compared to control, however, the knowledge only arm was $660 less expensive and, the combined arm was $3,630 less expensive than the control arm to achieve a 0.6% decrease in HbA1c.

Conclusions: Combined with the clinical findings, these results suggest telephone-delivered education and behavioral skills training is a cost-effective way to improve glycemic control. In particular, the combined knowledge and skills training intervention arm resulted in costs $3,630 lower than the control, and dropped HbA1c by 0.6%, achieving a clinically significant change for lower cost.

Supported By: National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases

Cost-Effectiveness Analysis of the EndoBarrier Device in Patients with Type 2 Diabetes

PIYAA SEN GUPTA, STEPHANIE ARMSTRONG, STEPHANIE A. AMIEL, ROBERT E. RYDER, MARK W. PENNINGTON, London, United Kingdom, Birmingham, United Kingdom

Objective: There are multiple pharmacotherapy options for type 2 diabetes mellitus (T2DM) including injectable glucagon-like peptide-1 receptor agonists (GLP-1RA) e.g., liraglutide. EndoBarrier is an innovative impermeable linear implant endoscopically into the proximal intestine for up to one year, before removal. We compared the cost effectiveness of three strategies in patients with suboptimally controlled diabetes despite at least 6 months’ liraglutide: EndoBarrier combined with 1.2mg liraglutide (E+L); EndoBarrier without liraglutide (E); and 1.8mg liraglutide with EndoBarrier (L) for the treatment of obese patients with T2DM from a National Healthcare perspective.

Methods: Seventy patients were randomised to one of three treatment arms (REVISE-Diabetes ISRCTN00151053) and followed for two years. Qual-
Cost as the Main Driver of T2D Treatment Patterns—Lessons from Real-World Data and Physician Focus Groups

This two-phased study consists of a decision tree model built from real-world claims data to determine factors related to physician choice of 2nd line therapy for type 2 diabetes (T2D) patients after metformin, followed by a physician focus group study to validate results of the data-driven approach.

Background: In total, 56% of physicians reported receiving feedback on their quality of diabetes care using performance measures that are inconsistent with diabetes care guidelines and national quality standards. Further, many physicians may not be strongly influenced by diabetes performance measurement. These discrepancies suggest that the impact of physician feedback on quality of diabetes care may be limited.

Conclusion: Ongoing educational support is vital in the early weeks of HCL. Improvement in HbA1c, RI=1 was 2 times more important than HbA1c (RI=0.3), and 10 times more important than age, comorbidity, and kidney status (GFR=RI=0.1). SU was most likely to be assigned to patients with lowest drug spending, moderate HbA1c control, abnormal kidney function, or no comorbid conditions. Similar themes were identified from the four physician focus groups (consisting of 8 endocrinologists and 10 PPs in NYC and LA) and supported the findings. This study identified a gap in diabetes care where patients often receive SU due to lack of access to other treatment options.

Table 1: Decision Tree and Focus Group Findings

<table>
<thead>
<tr>
<th>Real-World Evidence</th>
<th>Focus Groups What these groups physicians use most*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalence</strong></td>
<td><strong>RR</strong></td>
</tr>
<tr>
<td><strong>2nd Line Therapy</strong></td>
<td><strong>Out-patient cost for diabetes medications</strong></td>
</tr>
<tr>
<td><strong>Meal Boluses</strong> (MMI)</td>
<td>High</td>
</tr>
<tr>
<td><strong>Correction Boluses</strong> (MC)</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>3.92**</td>
</tr>
<tr>
<td><strong>Year of MI</strong> (2005-2012)</td>
<td></td>
</tr>
<tr>
<td><strong>Medication strategy</strong></td>
<td>No other pre-medication treatment**</td>
</tr>
<tr>
<td><strong>Diabetes care</strong></td>
<td>Physician in consultations such as checklists</td>
</tr>
<tr>
<td><strong>Care integration</strong></td>
<td>Integrated diabetes care using performance measures that are inconsistent with diabetes care guidelines and national quality standards. Further, many physicians may not be strongly influenced by diabetes performance measurement. These discrepancies suggest that the impact of physician feedback on quality of diabetes care may be limited.</td>
</tr>
</tbody>
</table>

**Note:** RI=1 was 2 times more important than HbA1c (RI=0.3), and 10 times more important than age, comorbidity, and kidney status (GFR=RI=0.1). SU was most likely to be assigned to patients with lowest drug spending, moderate HbA1c control, abnormal kidney function, or no comorbid conditions. Similar themes were identified from the four physician focus groups (consisting of 8 endocrinologists and 10 PPs in NYC and LA) and supported the findings. This study identified a gap in diabetes care where patients often receive SU due to lack of access to other treatment options.
Basal-Bolus Insulin Therapy May Not Be the Optimal Strategy in a “Real-World” Hospital Setting for Inpatient Hyperglycemia Management
ARCHANA R. SADHUA, BHARGAVI PATHAM, AISHA VADHARIYA, MICHAEL L. JOHNSON, Houston, TX
Basal bolus insulin therapy (BB) is recommended for glucose control in noncritically ill inpatients based on two small RABBIT2 trials. However, BB is complex and has limited data in large scale “real world” settings. This is a retrospective analysis of 4,558 noncritical, medical-surgical admissions from 1/2013 to 9/2015 in patients ≥18 years who received SC but not IV insulin for ≥75% of the stay. Insulin therapy was identified within the first 2 days as BB (long + rapid, n=2,319), sliding scale (SS, rapid only, n=1,855) or Basal Only (BO, long only, n=384). A propensity score analysis adjusted for clinical, demographic and physician variables affecting choice of therapy. Point of care glucose (mg/dl) was used to define patient days as hypo- (any <70), hyper- (mean >180) or euglycemic (no <70 AND mean ≤180). Negative binomial regression analyzed glucose outcomes (number of hypo-, hyper- and euglycemic days, mean glucose), linear regression modeled log of length of stay (LOS); logistic regression modeled odds of 30 and 60 day readmission. All analyses were conducted overall and by medical or surgical DRG. BB had worse glucose control but less LOS in medical DRG. BO had better hyper-, euglycemic and mean glucose. BB and BO had more hypo- days. This suggests that BB may be superior and simpler than SS for hyperglycemia but medical patients may benefit from BB for reasons beyond glucose control.

Table. Insulin groups OVERALL (n=4,558) MEDICAL DRG (n =3,211) SURGICAL DRG (n =1,347) Length of stay* BB vs. SS 0.97 (0.141) 0.94 (0.003) 1.02 (0.040) BO vs. SS 1.01 (0.711) 0.99 (0.741) 1.03 (0.665) Hyperglycemic days* BB vs. SS 0.99 (0.700) 0.97 (0.416) 1.00 (0.922) BO vs. SS 0.69 (<0.001) 0.69 (<0.001) 0.69 (<0.001) Hypoglycemic days* BB vs. SS 2.45 (<0.001) 2.29 (<0.001) 2.78 (<0.001) BO vs. SS 2.71 (<0.001) 2.37 (<0.001) 3.40 (<0.001) Euglycemic days* BB vs. SS 0.91 (0.008) 0.85 (<0.001) 1.01 (0.823) BO vs. SS 1.15 (0.012) 1.11 (0.151) 1.20 (0.083) Mean glucose* BB vs. SS 1.01 (0.415) 1.69 (0.266) -1.18 (0.589) BO vs. SS -17.27 (<0.001) -17.95 (<0.001) -15.91 (<0.001) 1. Results for 30 and 60 day readmission are not significantly different across the groups and are not presented in the Table; 2. Results above shown as: Estimate (p-value).

Improving Multidisciplinary Care in Pediatric Diabetes Clinic
DANIEL J. DESALVO, SARA K. BARTZ, CURTIS YEE, RONA SONABEND, Houston, TX
Background: A team-based approach facilitates comprehensive assessment and individualized care plan for diabetes patients. The ADA recommends diabetes patients see a Certified Diabetes Educator (CDE), Registered Dietician (RD) and Social Worker (SW) at least once yearly. Prior to this QI project, diabetes patients may benefit from BB for reasons beyond glucose control.

Drug Copay and Hospitalizations in Elderly Patients with Type 2 Diabetes
LIOU XU, MANJURI PAWASKAR, YUEXIN TANG, GARY FUCKREIN, SWAPNIL RAJPATHAK, BRUCE C. STUART, Washington, DC; North Wales, PA; Baltimore, MD
Prior studies have shown that higher drug copay may be associated with a lower adherence and higher healthcare resource utilization in type 2 diabetes (T2D) patients but mostly in younger commercially insured population. Hence the current study examined this association in elderly T2D patients. This retrospective database study used Medicare claims database included T2D patients on branded moninsulin anti-hyperglycemic

ADA-Supported Research Moderated Poster Discussion

HEALTH CARE DELIVERY—ECONOMICS/QUALITY IMPROVEMENT

1257-P

1258-P

Delays in Antihyperglycemic Treatment Intensification and Risk of Diabetes Complications
GREGORY NICHOLS, VICTORIA J. ROMO-LETOURNEAU, SUMA YUPPUTURI, SHEILA THOMAS, Portland, OR, ENCINITAS, CA, ROCKVILLE, MD, Bridgewater, NJ
Longer delays in anti-hyperglycemic treatment intensification (TI) are associated with poorer glycemic control, but whether these delays increase the risk of poor outcomes is unclear. We combined 2005-2016 data from the Northwest and Mid-Atlantic regions of Kaiser Permanente to identify 3 cohorts of patients who intensified therapy by: i) initiating metformin (MET) as their 1st diabetes drug (n=18,762), 2) adding a sulfonylurea (SU) to existing MET (n=10,076), 3) initiating insulin after MET and/or SU therapy (n=9,778). We used the TI date to calculate time between A1C >7% and TI, pre-TI A1C, and achievement of A1C <7% within 1 year. From the 1-year post-TI A1C, we followed patients through December 2016 until they experienced an MI, stroke, or other cardiovascular (CV) event, a heart failure (HF) hospitalization or all-cause mortality, censoring follow-up when the cohort therapy changed. Multivariable cox regression controlled for CV risk factors including age, sex, race/ethnicity, smoking, blood pressure, statin and ACE/ARB use, and prior history of CV or HF. After adjustment for CV risk factors, Pre-TI A1C and time from A1C ≥7% to TI date was significantly associated with the outcomes (Table). Delays in treatment intensification increase CV, HF and mortality risk at all stages of diabetes therapy; intensifying therapy at the first sign of deteriorating glycemic control may be critically important.

Table. Hazard Ratios (95% Confidence Intervals).

<table>
<thead>
<tr>
<th>Pre-Intensification A1C</th>
<th>Metformin Cohort</th>
<th>Sulfonylurea Cohort</th>
<th>Insulin Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular Event</td>
<td>1.10 (1.03-1.16)</td>
<td>1.03 (0.96-1.10)</td>
<td>1.09 (1.04-1.13)</td>
</tr>
<tr>
<td>Heart Failure Hospitalization</td>
<td>1.07 (1.01-1.14)</td>
<td>1.05 (0.99-1.13)</td>
<td>0.99 (0.96-1.03)</td>
</tr>
<tr>
<td>All-cause Mortality</td>
<td>1.07 (1.01-1.14)</td>
<td>1.06 (0.99-1.13)</td>
<td>0.99 (0.96-1.02)</td>
</tr>
</tbody>
</table>

Months to Intensification

| Cardiovascular Event    | 1.02 (0.95-1.09) | 1.05 (1.00-1.11) | 1.04 (1.00-1.08) |
| Heart Failure Hospitalization | 1.06 (1.00-1.13) | 1.05 (0.99-1.12) | 1.00 (0.97-1.03) |
| All-cause Mortality      | 1.06 (1.00-1.13) | 1.06 (1.00-1.12) | 1.00 (0.97-1.03) |

ADA-Supported Research Moderated Poster Discussion

A337
Table: Relative risk for hospitalization by branded medication copay categories in elderly patients with type 2 diabetes (T2DM).

<table>
<thead>
<tr>
<th>Drug copay categories (reference: &lt;$10)</th>
<th>Relative risk (RR)</th>
<th>95% Confidence Interval (CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;$10</td>
<td>1.01</td>
<td>0.89-1.16</td>
<td>0.893</td>
</tr>
<tr>
<td>$10-$30</td>
<td>1.13</td>
<td>0.99-1.29</td>
<td>0.061</td>
</tr>
<tr>
<td>$30-$50</td>
<td>1.12</td>
<td>0.99-1.27</td>
<td>0.076</td>
</tr>
<tr>
<td>$50-$100</td>
<td>1.14</td>
<td>1.00-1.29</td>
<td>0.044</td>
</tr>
<tr>
<td>$100+</td>
<td>1.12</td>
<td>1.05-1.28</td>
<td>0.272</td>
</tr>
<tr>
<td>≥$100</td>
<td>1.17</td>
<td>1.04-1.34</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Notes: Poisson regression model was adjusted for baseline patient characteristics including demographics, comorbidities, prior healthcare utilization, and geographic location.

Supported By: Merck & Co., Inc.

Factors Associated with Secondary Nonadherence to Oral Anti-hyperglycemic Agents among Patients with T2DM

SHARON LARSON, YUEXIN TANG, H. LESTER KIRCHNER, Wynnewood, PA, North Wales, PA, Danville, PA

Glycemic control in patients with T2DM remains sub-optimal. A major contributor to poor goal achievement is medication nonadherence. This study aimed to examine secondary nonadherence to oral anti-hyperglycemic agents (AHA) among T2DM patients and to assess its association with community- and individual-level characteristics.

Using claims and electronic medical records in Geisinger Health System during 2003-2015, this retrospective cohort study included adults with newly diagnosed T2DM who filled their 1st order of oral AHA. Secondary nonadherence was determined when patients did not fill the 2nd oral AHA prescription within 30 days after the 1st fill supply ended.

Among 2,413 patients who filled the 1st order, 764 (31.7%) were not adherent to the 2nd prescription. Younger age, non-white (vs. white) and chronic kidney disease was associated with higher odds of nonadherence. Patients with higher baseline HbA1c when ≤ 10% was associated with lower odds of nonadherence, while those with higher baseline HbA1c when >10% were more likely to be non-adherent. Community-level characteristics were not found to be associated with nonadherence.

Nearly one-third of patients did not complete a 2nd fill of their oral AHA. This study identified patient characteristics associated with secondary non-adherence that may provide intervention points for improving medication adherence in diabetes management.

Table: Logistic Regression of Secondary Nonadherence to Oral Anti-Hyperglycemic Agents

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.99 (0.98, 0.998)</td>
<td>0.0152</td>
</tr>
<tr>
<td>White Race</td>
<td>0.50 (0.30, 0.84)</td>
<td>0.0091</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>0.78 (0.59, 1.05)</td>
<td>0.0628</td>
</tr>
<tr>
<td>≥1 ED Visit in Prior 12 Months</td>
<td>1.27 (0.98, 1.66)</td>
<td>0.0718</td>
</tr>
<tr>
<td>1st Medication Order: Metformin</td>
<td>0.83 (0.67, 1.03)</td>
<td>0.0935</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>1.97 (1.05, 3.76)</td>
<td>0.0411</td>
</tr>
<tr>
<td>HbA1C ≤10%</td>
<td>0.83 (0.76, 0.91)</td>
<td>0.0204</td>
</tr>
<tr>
<td>HbA1C &gt;10%</td>
<td>1.14 (1.01, 1.30)</td>
<td>0.0736</td>
</tr>
</tbody>
</table>

Notes: ED=emergency department; All variables significant at the p<0.05 level in bivariate analysis were considered in the logistic regression model. Baseline HbA1c exhibited a non-linear relationship with secondary nonadherence. Therefore, linear splines with a knot at 10% was used in this model to allow for a different slope of HbA1c ≤10% and >10%.

Supported By: Merck & Co., Inc.
Severe Hypoglycemia (SH) and Diabetic Ketoacidosis (DKA) Hospitalization Rates—Twenty-Five Years in the Epidemiology of Diabetes Complications (ECD) Study

GEORGINA PAMBIANCO, TREVOR J. ORCHARD, Pittsburgh, PA

SH and DKA are common serious acute complications of type 1 diabetes (T1D), but whether rates have changed with recent improvements in diabetes management is not clear. We, thus examined data from the Pittsburgh Epidemiology of Diabetes Complications (ECD) study of childhood onset T1D (mean age 28 and duration 19 years, n=656) to determine if the hospitalized rates of SH and DKA have changed over 25 years of follow-up. Participants reported hospitalizations at each biennial survey for the prior 5 years (1986-1998, 2012-2014) or prior 3 years (1996-1999, 2004-2006). Rates per 100 person years for SH and DKA were then calculated by dividing the total number of self-reported SH or DKA admissions by the total appropriate accumulated person years of reporting at each follow-up. Hospitalization rates for SH declined after 1996-1998 with a fall in HbA1c suggesting better overall management. The DKA hospitalization rate was consistent throughout the follow-up. The factors underlying these encouraging trends require further investigation and survival bias cannot be excluded.

Cost Effectiveness of DPP-4i and SGLT2i Combination Therapy for the Treatment of Type 2 Diabetes in the U.S.

MANJIRI PAWASKAR, S. PINAR BILIR, ANNA GRABER-NAIDCH, CLAUDIO D. GONZALEZ, SWAPNIL RAJPATIKA, GLENN M. DAVIES, North Wales, PA, San Francisco, CA, Kenilworth, NJ

Management of type 2 diabetes (T2D) needs different treatment strategies to achieve the individualized glycemic goal. This study evaluated the long-term cost effectiveness of strategies involving pathway 1: Metformin followed by intensification with dipeptidyl peptidase-4 inhibitors (DPP-4i), sodium-glucose co-transporter 2 inhibitors (SGLT2i) and insulin vs. pathway 2: Metformin followed by intensification with sulfonylurea (SU) and insulin in the U.S. Cost-effectiveness analysis was performed using the validated QuintilesIMS CORE Diabetes Model from a U.S. payer perspective. Clinical and economic outcomes were modeled over a lifetime for a cohort of T2D patients who fail to achieve glycemic goal on metformin monotherapy. Clinical data were obtained from clinical trials. Direct medical costs [e.g., medications (whole sale acquisition costs), diabetes management, adverse events, and complications] were obtained from published sources. Despite higher direct medical costs for pathway 1 compared to pathway 2 ($117,779 vs. $93,196 respectively), pathway 1 improved total quality-adjusted life years (QALY) by 0.28 vs. pathway 2. Pathway 1 also led to cost offsets from fewer diabetes-related complications and delayed initiation of insulin. The incremental cost-effectiveness ratio (ICER) was favorable for pathway 1 at $89,038/QALY. Most of the scenario analysis (changes in treatment effect, hypoglycemia, and cardiovascular protective effects of SGLT2is) resulted in ICERs under $100,000/QALY except for the population with baseline HbA1c of 7%, and older age (65+ years). Negotiated discounts on branded medications resulted in significant improvement in ICERs (ICER of $69,554/QALY for 15% discount and $0/QALY for 75% discount). Among patients failing metformin monotherapy in the U.S, additional intensification with DPP-4i followed by SGLT2i may be considered more cost effective compared to intensified with SU followed by insulin.

Cost Effectiveness of DPP-4i and SGLT2i Combination Therapy for the Treatment of Type 2 Diabetes in the U.S.

MANJIRI PAWASKAR, S. PINAR BILIR, ANNA GRABER-NAIDCH, CLAUDIO D. GONZALEZ, SWAPNIL RAJPATIKA, GLENN M. DAVIES, North Wales, PA, San Francisco, CA, Kenilworth, NJ

Management of type 2 diabetes (T2D) needs different treatment strategies to achieve the individualized glycemic goal. This study evaluated the long-term cost effectiveness of strategies involving pathway 1: Metformin followed by intensification with dipeptidyl peptidase-4 inhibitors (DPP-4i), sodium-glucose co-transporter 2 inhibitors (SGLT2i) and insulin vs. pathway 2: Metformin followed by intensification with sulfonylurea (SU) and insulin in the U.S. Cost-effectiveness analysis was performed using the validated QuintilesIMS CORE Diabetes Model from a U.S. payer perspective. Clinical and economic outcomes were modeled over a lifetime for a cohort of T2D patients who fail to achieve glycemic goal on metformin monotherapy. Clinical data were obtained from clinical trials. Direct medical costs [e.g., medications (whole sale acquisition costs), diabetes management, adverse events, and complications] were obtained from published sources. Despite higher direct medical costs for pathway 1 compared to pathway 2 ($117,779 vs. $93,196 respectively), pathway 1 improved total quality-adjusted life years (QALY) by 0.28 vs. pathway 2. Pathway 1 also led to cost offsets from fewer diabetes-related complications and delayed initiation of insulin. The incremental cost-effectiveness ratio (ICER) was favorable for pathway 1 at $89,038/QALY. Most of the scenario analysis (changes in treatment effect, hypoglycemia, and cardiovascular protective effects of SGLT2is) resulted in ICERs under $100,000/QALY except for the population with baseline HbA1c of 7%, and older age (65+ years). Negotiated discounts on branded medications resulted in significant improvement in ICERs (ICER of $69,554/QALY for 15% discount and $0/QALY for 75% discount). Among patients failing metformin monotherapy in the U.S, additional intensification with DPP-4i followed by SGLT2i may be considered more cost effective compared to intensified with SU followed by insulin.

Cost Effectiveness of DPP-4i and SGLT2i Combination Therapy for the Treatment of Type 2 Diabetes in the U.S.

MANJIRI PAWASKAR, S. PINAR BILIR, ANNA GRABER-NAIDCH, CLAUDIO D. GONZALEZ, SWAPNIL RAJPATIKA, GLENN M. DAVIES, North Wales, PA, San Francisco, CA, Kenilworth, NJ

Management of type 2 diabetes (T2D) needs different treatment strategies to achieve the individualized glycemic goal. This study evaluated the long-term cost effectiveness of strategies involving pathway 1: Metformin followed by intensification with dipeptidyl peptidase-4 inhibitors (DPP-4i), sodium-glucose co-transporter 2 inhibitors (SGLT2i) and insulin vs. pathway 2: Metformin followed by intensification with sulfonylurea (SU) and insulin in the U.S. Cost-effectiveness analysis was performed using the validated QuintilesIMS CORE Diabetes Model from a U.S. payer perspective. Clinical and economic outcomes were modeled over a lifetime for a cohort of T2D patients who fail to achieve glycemic goal on metformin monotherapy. Clinical data were obtained from clinical trials. Direct medical costs [e.g., medications (whole sale acquisition costs), diabetes management, adverse events, and complications] were obtained from published sources. Despite higher direct medical costs for pathway 1 compared to pathway 2 ($117,779 vs. $93,196 respectively), pathway 1 improved total quality-adjusted life years (QALY) by 0.28 vs. pathway 2. Pathway 1 also led to cost offsets from fewer diabetes-related complications and delayed initiation of insulin. The incremental cost-effectiveness ratio (ICER) was favorable for pathway 1 at $89,038/QALY. Most of the scenario analysis (changes in treatment effect, hypoglycemia, and cardiovascular protective effects of SGLT2is) resulted in ICERs under $100,000/QALY except for the population with baseline HbA1c of 7%, and older age (65+ years). Negotiated discounts on branded medications resulted in significant improvement in ICERs (ICER of $69,554/QALY for 15% discount and $0/QALY for 75% discount). Among patients failing metformin monotherapy in the U.S, additional intensification with DPP-4i followed by SGLT2i may be considered more cost effective compared to intensified with SU followed by insulin.

Cost Effectiveness of DPP-4i and SGLT2i Combination Therapy for the Treatment of Type 2 Diabetes in the U.S.

MANJIRI PAWASKAR, S. PINAR BILIR, ANNA GRABER-NAIDCH, CLAUDIO D. GONZALEZ, SWAPNIL RAJPATIKA, GLENN M. DAVIES, North Wales, PA, San Francisco, CA, Kenilworth, NJ

Management of type 2 diabetes (T2D) needs different treatment strategies to achieve the individualized glycemic goal. This study evaluated the long-term cost effectiveness of strategies involving pathway 1: Metformin followed by intensification with dipeptidyl peptidase-4 inhibitors (DPP-4i), sodium-glucose co-transporter 2 inhibitors (SGLT2i) and insulin vs. pathway 2: Metformin followed by intensification with sulfonylurea (SU) and insulin in the U.S. Cost-effectiveness analysis was performed using the validated QuintilesIMS CORE Diabetes Model from a U.S. payer perspective. Clinical and economic outcomes were modeled over a lifetime for a cohort of T2D patients who fail to achieve glycemic goal on metformin monotherapy. Clinical data were obtained from clinical trials. Direct medical costs [e.g., medications (whole sale acquisition costs), diabetes management, adverse events, and complications] were obtained from published sources. Despite higher direct medical costs for pathway 1 compared to pathway 2 ($117,779 vs. $93,196 respectively), pathway 1 improved total quality-adjusted life years (QALY) by 0.28 vs. pathway 2. Pathway 1 also led to cost offsets from fewer diabetes-related complications and delayed initiation of insulin. The incremental cost-effectiveness ratio (ICER) was favorable for pathway 1 at $89,038/QALY. Most of the scenario analysis (changes in treatment effect, hypoglycemia, and cardiovascular protective effects of SGLT2is) resulted in ICERs under $100,000/QALY except for the population with baseline HbA1c of 7%, and older age (65+ years). Negotiated discounts on branded medications resulted in significant improvement in ICERs (ICER of $69,554/QALY for 15% discount and $0/QALY for 75% discount). Among patients failing metformin monotherapy in the U.S, additional intensification with DPP-4i followed by SGLT2i may be considered more cost effective compared to intensified with SU followed by insulin.
Clinical Diabetes/Therapeutics

code, aged
mia were 4-23%, which was higher than expected. Patients with HbA1c val-

of diabetes status. Data were collected for insulin orders, administration

Medical Center from March to September 2017. Patients included adults on

ment.

have shown widespread use. The aim of this project was to identify current

mend against using correctional insulin alone; however, previous surveys

with diabetes; glucose ranges of 80-180mg/dL are acceptable. They recom-

San Antonio

Institutional Inpatient Diabetes Management—We’re Still Not

1268-P

Impact of a Structured Patient-Support Program on Adherence and

Persistency with Basal Insulin Therapy at 12 Months

FANG L. ZHOU, JASON YEAW, SWAPNA KARKARE, MITCH DEKOVEN, TIMOTHY
S. Reid, Bridgewater, NJ; Denver, CO; Deerfield, IL; Fairfax, VA; Janesville, WI

The COACH patient-support program was launched in 2015 to support and

ducate patients prescribed insulin glargine 300 U/mL (Gla-300). The study

objective was to assess program impact on adherence and persistence among

patients with T2D on Gla-300 therapy.

A retrospective cohort study was conducted, linking data from COACH

to patient data in the IQVIA Integrated Data Warehouse. Overall inclusion cri-

tera for patients identified from 2/1/2016-3/31/2016 were: ≥1 T2D diagnosis
code, age ≥18 years, ≥1 pharmacy claim for Gla-300 (first claim as index
date), continuous database activity for ≥180 days preceding the 6-month

pre-index, and pharmacy stability in the 6-month pre-index. Exclusion cri-
tera were: ≥1 pharmacy claim for another basal insulin ≤14 days preceding

index, and data-quality issues. Patients from the COACH Participant cohort

(active participants of the program) were directly matched to a Non-COACH
cohort of patients not enrolled in COACH. Patients who were insulin naïve,

switched from any other basal insulin to Gla-300, and with high levels of

glucose control remained poor. Troublingly, 13% of patients receiving correctional

insulin alone had normoglycemia or normal baseline HbA1c values; 19% of

these patients developed hypoglycemia during hospitalization.

Conclusion: Despite national guidelines, the majority of patients in our

institution received only correctional insulin and did not achieve glucose

targets. Additionally, most patients receiving basal/bolus insulin did not

achieve glucose targets, suggesting inadequate titration. This requires sys-

tematic interventions to improve inpatient diabetes management.

Disclaimer: The views expressed are those of the authors and do not reflect

the official views or policy of the Department of Defense or its Components.

1269-P

Characterization of Patients Requiring High-Dose Insulin Infusion

for the Management of Hyperglycemia

AFOAMIA A. FELEKE, RACHAEL C. FULLER, REEM ISMAIL, MEGAN CADIZ, Royal

Oak, MI

There are several validated insulin infusion protocols to help guide intra-

venous (IV) insulin dose titrations. However, when continued upward titra-

tion of insulin infusion is required to achieve glycemic control, little is known
to guide how high the infusion rate can be increased without compromising

safety and improving efficacy. The purpose of this study was to characterize

patients requiring high-dose insulin infusions (rates ≥20 units/hour) for the

management of hyperglycemia and determine the incidence at our institu-

tion. A retrospective chart review of all patients aged 18 years or older who

received IV insulin infusion between 01/01/2016 and 03/31/2017 at Beaumont

Hospital, MI resulted in 82 patients (2.9%) who received high-dose insulin

infusion for the management of hyperglycemia. Average age was 82 years

old and majority were Caucasian males. Most patients had hyperglycemia

associated with risk factors such as: history of type 2 diabetes (71%), obesity
(median body mass index (BMI) was 33.9 kg/m²), critical illness (89%), many

were surgical patients (≥50%), and a large proportion received vaspressors
(79%) and corticosteroids (36%). The highest infusion rate observed was 80

units/hour, with a median infusion rate of 6.5 units/hour. Hypoglycemia (BG ≤70

mg/dL) was reported in 29% of patients and 11% had recurrent hypoglyce-

mic episodes. Our findings suggest that the overall need for high-dose insulin

infusion rates is very low. However, the incidence of hypoglycemia in these

patients was substantially high and therefore concerning. Insulin is a high-

alert medication requiring implementation of appropriate safety measures

to prevent errors and careful investigation is warranted when used in high-

doses. We recommend an insulin infusion “time-out” to assess the infusion

site, the IV line and insulin bag before exceeding 20 units/hour. Furthermore,

institutional policies for soft- and hard-maximum infusion parameters should

be established to conserve use.

1270-P

Preserving Vision by Empowering Patients

ALMIRA J. YANG, VAN T. LA, CHIBUZO U. EKE, ANTHONY FIREK, Moreno Valley, CA, Riverside, CA

Diabetic retinopathy (DR) is a preventable complication of diabetes with early
detection and intervention. Prior studies have shown patient engagement

and empowerment improve patient knowledge and self-care resulting in

better outcomes. Yet, screening and treatment of DR remain a major chal-

lenge especially in our underserved, indigent patient populations. Graphical

education material is often used to improve detection of DR but its effec-
tiveness is rarely assessed, especially in the underserved. To improve DR

screening in our population, we developed a quality improvement project

using in-clinic graphic material to empower patients to screen for DR, fol-

lowed by post clinic surveys to evaluate the impacts on screening rates and

patient engagement.

Posters in English and Spanish were placed in primary care clinics directly

viewed by patients for 3 months. We surveyed 100 patients and 12 provid-

ers to evaluate the effectiveness of the intervention. We reviewed 84 and

200 charts to determine both pre- and post-intervention DR screening rates.

No difference was seen in the DR screening rate between the pre- and

post-intervention periods (51.0% vs. 50.0%, p = 0.88). There were improve-

ments in the referral rate and the retinal exam visit rate between pre- and

post-intervention periods (76.2% vs. 82.2%, p = 0.142; 63.9% vs. 73.3%,
p = 0.048, respectively). Among the 49 patients who saw educational post-

ers, 69% reported the posters prompted them to discuss with the provid-

ers about retinal screening exams.

Our study demonstrated that posters can improve patients’ awareness of

DR leading to positive engagement with their providers, and eventually

improve DR screening efforts. However, multiple factors such as patient lit-

eracy, limited encounter time, and understanding may limit the effectiveness

HEALTH CARE DELIVERY—ECONOMICS/QUALITY IMPROVEMENT

Clinical Diabetes/Therapeutics

POSTERS

A340

Moderated Poster Discussion 
ADA-Supported Research
of education interventions particularly in our underserved patients. As DR particularly impacts this population, more innovative and direct interactions may need to be implemented to improve self knowledge and patient empowerment to improve DR screening.

1271-P

**WITHDRAWN**

**Assessing the Value of Canagliflozin (CANA) vs. Sitagliptin (SITA) as Second-Line Therapy in the U.S.—The Importance of Considering Evidence from the CANVAS Program**

MICHAEL WILLIS, CHERYL NESLUSAN, ANDREAS NILSSON, CHRISTIAN ASSEBURG, Lund, Sweden; Raritan, NJ

Efficient allocation of health care resources requires choosing treatments that provide good “value for money,” which for chronic and progressive diseases like diabetes requires long-term modeling. For patients not controlled on metformin (MET), the ADA’s Standards of Medical Care recommend that “drug-specific effects and patient factors” guide the choice of next agent and that those with atherosclerotic CVD receive treatment with agents with evidence of CV risk reduction. The SGLT2 inhibitors CANA and empagliflozin have shown such a benefit, unlike the DPP-4s. The objective of this analysis was to estimate the cost-effectiveness of CANA vs. SITA as add-on to MET from the U.S. 3rd party payer perspective. A comprehensive health economics model (ECHO-T2DM) was used to estimate health and cost consequences over 30 years. Baseline patient characteristics and biomarker changes were sourced from a previously reported head-to-head study of CANA vs. SITA as add-on to MET. Hazard ratios from the CANVAS Program for myocardial infarction (MI), stroke, heart failure hospitalization, and CV mortality were used to capture effects not mediated by changes in biomarkers (i.e., HbA1c). The model was calibrated to preserve the ratio of the observed cumulative incidence of stroke between treatment arms. Finally, results were extrapolated over 50 years. The UKPDS 68 equations were able to predict 64% of the observed 2-year stroke risk reduction, suggesting a drug-mechanistic effect other than changes in risk factors. Calibration results indicate that a relative risk of stroke of 0.83 (17% reduction) applied to once-weekly semaglutide was required to preserve the cumulative incidence ratio. Results of extrapolation increased quality-adjusted life-years by 0.18 and life-years by 0.29 vs. placebo+SoC. Results of this analysis may have implications on future approaches assessing the long term economic impact of new therapies in T2D in this era of multiple CVOts.

1273-P

**Incorporating Cardioprotective Effects of Once-Weekly Semaglutide in Estimates of Health Benefits for Patients with Type 2 Diabetes**

MARC EVANS, PIERRE JOHANSEN, HRVOJE VRAZIC, Cardiff, United Kingdom; Sabang, Denmark

Economic modeling of type 2 diabetes (T2D) relies on sets of risk equations (e.g., UKPDS 88) to predict cardiovascular (CV) events and mortality as mediated through changes in risk factors (e.g., HbA1c). Recent CV outcomes trials (CVOts) have shown significant benefits in events over a short time period (between 2-4 years), along with beneficial changes in risk factors such as blood pressure, HbA1c, and weight. The contributions of these changes to the observed outcomes within these CVOts are unclear. In patients with high CV risk, the SUSTAIN 6 trial of once-weekly semaglutide+standard of care (SoC) reported a statistically significant reduction in stroke (HR=0.61) after 104 weeks vs. placebo+SoC. We sought to establish the contribution of risk factor changes to this observed outcome, by evaluating the performance of traditional risk equations in predicting outcome benefits seen with once-weekly semaglutide. As a secondary objective, the impact of incorporating the stroke benefit on estimated long term health benefits was assessed. The IGWA Core Diabetes Model was used to assess predictive accuracy of the UKPDS 68 risk equations on the observed stroke benefit. Secondly, the model was calibrated to preserve the ratio of the observed cumulative incidence of stroke between treatment arms. Finally, results were extrapolated over 50 years. The UKPDS 68 equations were able to predict 64% of the observed 2-year stroke risk reduction, suggesting a drug-mechanistic effect other than changes in risk factors. Calibration results indicate that a relative risk of stroke of 0.83 (17% reduction) applied to once-weekly semaglutide was required to preserve the cumulative incidence ratio. Results of extrapolation increased quality-adjusted life-years by 0.18 and life-years by 0.29 vs. placebo+SoC. Results of this analysis may have implications on future approaches assessing the long term economic impact of new therapies in T2D in this era of multiple CVOts.
1275-P
Electronic Messaging Use via a Patient Portal Is Associated with Primary Care Utilization in Patients with Type 2 Diabetes

RAN SUN, SUSAN M. SEREika, MELISSA SAUL, MARY T. KORYtkowski, DAN LI, LURA E. BURKE, Pittsburg, PA

Background: Electronic messaging via a patient portal is being used with increasing frequency for patient-provider communication, especially for the ongoing management of type 2 diabetes (T2DM). Providing patients online access to providers may reduce the need for face-to-face contact; yet little is known about the usage pattern and its association with the frequency of office visits to primary care providers (PCP).

Methods: A cross-sectional analysis was conducted using the data from the ambulatory electronic health records of UPMC Physicians Services. Adults with T2DM who were seen in UPMC PCP offices between Jan. 2015 and Dec. 2016 were included. The number of days messaging was used, and the number of PCP visits for each patient were calculated during the study period. Descriptive statistics were applied. Negative binomial regression was performed to examine the association of messaging use with the number of PCP visits, adjusting for age, gender, race, education, income, insurance type, and the number of comorbidities.

Results: The prevalence of patients who used messaging was 85.5% and 49.9% female with a mean age of 65.2±11.9 years. About a third (36.7%, n=15,698) used the messaging feature at least once during the study period. The median number of days that used the messaging feature was 13.0 (range 1-395). Negative binomial regression revealed that greater use of messaging was associated with a greater number of PCP visits (Incidence Rate Ratio 1.0014, 95% CI, 1.0011-1.0018).

Conclusion: In our study, over one-third of the patients used the messaging feature via the portal. More frequent use of messaging was associated with a greater number of PCP visits, suggesting that both measures represent patient engagement in health care services. However, the frequency of PCP visits may not be an accurate indicator of clinical outcomes. Future studies that include patient outcome measures, such as HbA1c, according to portal use are needed as use of this technology increases.

1276-P
Medical Costs of Diabetic Ketoadidosis Presenting at Diagnosis of Diabetes among Privately Insured Youth, 2016

SUNDAR SHRESTHA, PING ZHANG, GIUSEPPINA IMPERATORE, Atlanta, GA

Diabetes ketoadidosis (DKA) is a potentially preventable acute and severe complication of diabetes (DM). Youth often present with DKA at DM diagnosis and having DKA predicts poor long-term glycemic control. Little is known about the medical costs associated with DKA presenting at DM diagnosis. Using 2010-2016 MarketScan claims data, we estimated the occurrence of DKA at DM diagnosis and compared medical costs 60 days prior and post DM diagnosis in youth (age <20 years) with and without DKA. We identified newly diagnosed DM as having ≥1 outpatient or ≥2 outpatient claims 30 days apart with DM codes, but no DM claim or prescription of DM medications in the two years prior to DM diagnosis, no history of acute/chronic pancreatitis, and no gestational DM. Both DM and DKA were identified using ICD9 or ICD10 claim codes. We estimated medical costs (in U.S. $2,016) using regression models (Table). Among 3,301 youth with newly diagnosed DM, 43% presented with DKA. As compared to youth without DKA, those with DKA were younger and more likely to be males (p<0.05). Health services use and total medical costs are presented in Table. The presence of DKA at DM diagnosis was associated with large financial burden to both the health care system (>86,500) and to patients (>1,100). These data could be used for planning and evaluating interventions aimed at preventing this life-threatening condition.

Table. Health Services Use and Medical Costs among Youth, 60 Days Prior and Post Diabetes Diagnosis by DKA Status at Diagnosis.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>60 Days Prior DM Diagnosis</th>
<th>60 Days Post DM Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With DKA</td>
<td>Without DKA</td>
</tr>
<tr>
<td>Mean Health Services use:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of outpatient visits</td>
<td>2.10</td>
<td>3.27</td>
</tr>
<tr>
<td>No. of office visits</td>
<td>1.06</td>
<td>1.39</td>
</tr>
<tr>
<td>No. of ER visits</td>
<td>0.27</td>
<td>0.07</td>
</tr>
<tr>
<td>No. of inpatient admissions</td>
<td>1.00</td>
<td>0.85</td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td>2.45</td>
<td>1.82</td>
</tr>
</tbody>
</table>

Notes: *p<0.05, **p<0.01, ***p<0.001, ESRD—End Stage Renal Disease; # Estimated using a generalized linear model with log link and gamma distribution; # Estimated using a two-part model: logistic regression and generalized linear model with log link and gamma distribution controlling for age and sex.

1277-P
Excess Medical Expenditures Associated with Diabetes-Related Complications among Adult Medicaid Enrollees in Eight U.S. States

BOON PENG NG, SUNDAR SHRESTHA, ROBIN SOIL, BRYCE SMITH, PING ZHANG, Chamblee, GA, Atlanta, GA

The financial burden imposed by diabetes on Medicaid is substantial. While most of this burden is due to treating diabetes-related complications, little information is available on how much Medicaid paid for those complications and variability by state. Using 2008-2012 Medicaid claims data, we estimated per-capita annual medical expenditures for treating selected diabetes-related acute and chronic complications among Medicaid enrollees. Our study population included adults aged 19-64 enrolled in fee-for-service plan from eight states with adequate sample size, stratified by eligibility criteria: disability vs. non-disability enrollees. Complication conditions were identified using ICD-9 codes and selected based on sufficient sample size to derive reliable estimates. We compared expenditures between those with and without selected complications to derive excess expenditures. Diabetes-related complications consumed a substantial amount of excess Medicaid health care resources across the eight states (Table). Excess expenditure levels varied by state, condition, and eligibility criteria, with ischemic heart disease and renal disease having the largest variation. Implementing effective diabetes prevention and control measures could reduce expenditures on complications.

Table. Estimated Per Capita Excess Annual Medical Expenditures among Adult Medicaid Enrollees Associated with Diabetes-Related Complications Aged 19-64 Years by Eligibility-Based Disability Status (at U.S. $ 2012).

Note: All excess expenditures are statistically significant (P < 0.01)

<table>
<thead>
<tr>
<th>AL</th>
<th>CA</th>
<th>CT</th>
<th>FL</th>
<th>IA</th>
<th>IL</th>
<th>NY</th>
<th>OK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disability based</td>
<td>Non-ESRD renal disease</td>
<td>Ischemic Heart Disease</td>
<td>Hypoglycemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropathy</td>
<td>Neurological disorders</td>
<td>Aged 19-64 Years</td>
<td>Aged 19-64 Years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$2,481</td>
<td>$4,442</td>
<td>$6,206</td>
<td>$7,747</td>
<td>$9,060</td>
<td>$10,532</td>
<td>$5,901</td>
<td></td>
</tr>
<tr>
<td>$7,932</td>
<td>$22,226</td>
<td>$15,255</td>
<td>$14,396</td>
<td>$15,424</td>
<td>$24,875</td>
<td>$34,002</td>
<td>$18,010</td>
</tr>
<tr>
<td>$14,203</td>
<td>$10,619</td>
<td>$7,068</td>
<td>$8,654</td>
<td>$12,382</td>
<td>$14,759</td>
<td>$21,283</td>
<td>$11,286</td>
</tr>
<tr>
<td>$5,940</td>
<td>$12,726</td>
<td>$16,888</td>
<td>$11,883</td>
<td>$12,474</td>
<td>$14,117</td>
<td>$18,165</td>
<td>$13,768</td>
</tr>
</tbody>
</table>

One or more selected complications

| $5,811 | $15,996 | $12,081 | $8,386 | $14,165 | $17,881 | $25,362 | $14,290 |

Non-disability based

| Neuropathy | Neurological disorders | Aged 19-64 Years |
| $3,981 | $4,786 | $6,752 | $4,445 | $5,236 | $6,761 | $7,454 | $6,799 |
| $5,178 | $17,488 | $10,171 | $7,417 | $9,014 | $10,954 | $24,683 | $13,953 |
| $4,178 | $14,906 | $10,587 | $7,393 | $15,017 | $14,369 | $30,066 | $12,200 |
| $6,984 | $8,472 | $11,687 | $7,279 | $9,851 | $15,765 | $20,225 | $11,162 |

One or more selected complications

| $4,789 | $10,742 | $9,794 | $6,385 | $9,118 | $10,368 | $19,649 | $10,015 |

Notes: *Non-ESRD renal disease identified based on ICD-9 codes for proteinuria/albunuria, nephritis, anemia in chronic kidney disease, acute kidney failure, and other renal diseases without including ESRD, dialysis and transplant; Ischemic heart disease was based on Chronic Conditions Data Warehouse algorithm. All complications were identified based on ICD-9 codes from the past studies; Medical expenditures were estimated using a generalized linear model with log link and gamma distribution, adjusted for age, sex, race/ethnicity, claims year and comorbidities. The excess medical expenditures associated with a diabetes-related complication were calculated as the difference in predicted expenditures for enrollees with and without the complication.
Improving Diabetes Outcomes in Rural Dominican Republic

ELIZABETH A. WALKER, HENRY J. DETHLEFS IV, RACHEL A. DOVID, CLYDE SCHECHETER, CHARLES FILipi, BRONx, NY; OMAHA, NE

The Dominican Republic (DR) is a Caribbean country of 10 million with estimated diabetes prevalence at ~11%. While the public health system has a diabetes program, there are few reliable surveillance data to portray diabetes outcomes in the DR. The HbA1c is not a widely available test for metabolic control in the DR. In 2010, a non-profit group, Chronic Care International (CCI), began a diabetes and hypertension program with 2 clinics in poor, rural DR. CCI developed a model of quality improvement for care and self-management with its Dominican medical team, including doctors, nurses and community health workers. We present process and outcome data collected over 6 years utilizing electronic medical records. In addition to quality improvement analyses, we fit a random-effects linear model to the data to assess trends over time. By May 2017, subjects (N=7,031) were adults: mean age 60.1 years, 45% men, 74% with DM2. Of those with diabetes (n=758), 76% had an HbA1c>9%, with 88% having had an HbA1c test done in the last 4 mos. 615 with hypertension, 64% had a BP < 140/90mmHg. In assessing trends over time, we found the modeled HbA1c trajectory for those with diabetes showed an average decline of 0.13 percentage points per year (95% CI 0.10-0.15) over 6 years. The modeled BMI trajectory for all subjects showed an average decline of 0.09 percentage points per year (95% CI 0.04-0.09) over 6 years.

In conclusion, the burden of ESRD due to T1D and T2D and the associated costs are significantly higher for other races for both T1D and T2D compared to whites.

In contrast to other races, T2D Hispanics with ESRD were not more costly than whites ($6,634 vs. $6,542). Similar results were seen for net paid costs taking into account cost-sharing. Average cost-sharing for all patients with ESRD was $730 (no diabetes) $1,177 (T1D) and $939 (T2D) per member/month respectively. In conclusion, the burden of ESRD due to T1D and T2D and the associated cost for T1D with ESRD were higher for Hispanics than for white Medicare enrollees.

Racial Disparities in the Burden of End-Stage Renal Disease due to Diabetes among Medicare Beneficiaries

NAMINO M. GLANTZ, JAN DUNCAN, TAMIM AHMED, DAVID KERR, Santa Barbara, CA; Glastonbury, CT

Diabetes disproportionately impacts minority populations in the United States. In particular, Hispanics are almost twice as likely as non-Hispanic whites to be diagnosed with diabetes and have higher rates of end-stage renal disease (ESRD) due to diabetes. We analyzed data from the Medicare 5% sample file by race/ethnicity for type 1 (T1D) and type 2 diabetes (T2D) to determine the economic burden of ESRD.

For the years 2012-13 we identified 1,397,933 enrollees from the publicly-available Medicare 5% sample > 65 years without Medicare Advantage coverage (HMO). The prevalence of T1D was 2.0% and 21.9% for T2D. ESRD affected 5.4% of the T1D and 1.3% of T2D populations. Rates of ESRD were significantly higher for other races for both T1D and T2D compared to whites.

Comparing costs, allowed amount (claims less discounts/ineligible charges) for treating ESRD was higher for T1D Hispanics than T1D whites ($6,946 vs. $8,332 per member/month, P<0.001). In contrast to other races, T2D Hispanics with ESRD were not more costly than whites ($6,634 vs. $6,542). Similar results were seen for net paid costs taking into account cost-sharing. Average cost-sharing for all patients with ESRD was $730 (no diabetes), $1,177 (T1D) and $939 (T2D) per member/month respectively.

In conclusion, the burden of ESRD due to T1D and T2D and the associated cost for T1D with ESRD were higher for Hispanics than for white Medicare enrollees.

Figure.

Supported By: Eli Lilly and Company

The Effectiveness of Text Message Support for Weight Loss to Reduce Diabetes Risk

HENRY FISCHER, SILVIA RAGHUNATH, JOSH DURRE, NATALIE RITCHIE, Denver, CO

Objective: To reach the estimated 84.1 million U.S. adults with prediabetes, lower-cost alternatives to the National Diabetes Prevention Program (NDPP) are needed, which is estimated to cost $500 per person. In a previous randomized controlled trial, we demonstrated efficacy of a 12-month text message support program (SMS4PreDM) in individuals with prediabetes. We now explore effectiveness in a pragmatic study in a healthcare system, in addition to calculating per-person costs of SMS4PreDM.

Research Design and Methods: English- and Spanish-speaking patients with diabetes risks (e.g., A1C 5.7-6.4) were referred by their healthcare providers and offered NDPP classes, SMS4PreDM, or both. This analysis focused on comparing weight outcomes among SMS4PreDM-only participants to a usual care control group of patients with diabetes risks who were not referred. As a pragmatic study, weights for both groups were collected from electronic health records at baseline and 12 months. Rates of achieving ≥3% weight loss were compared using logistic regression, including a sub-analysis by language.

Results: Among 183 SMS4PreDM-only participants, 51.4% (N=94) had documented pre- and post-intervention weights and 30.9% (N=29) achieved ≥3% weight loss, compared with 23.4% of 1,871 control patients (p=0.10). English-speakers receiving SMS4PreDM trended toward ≥3% weight loss at a higher rate than English-speaking controls (36.5% vs. 25.6%, p=0.07). There was no significant difference among Spanish-speakers. In an intention-to-treat analysis that assumed no weight loss among participants with missing data, there was no significant difference in achieving ≥3% weight loss as compared to controls (20.8% vs. 20.2%, p=0.49). Costs of SMS4PreDM were $100.92 per capita.

Conclusions: SMS4PreDM trends toward greater achievement of ≥3% weight loss compared to usual care and at a lower cost than the NDPP. However, results may not be sufficiently robust or generalizable to support long-term implementation.

Supported By: Colorado Department of Public Health & Environment

ADA-Supported Research  Moderated Poster Discussion

A343
Clinical Diabetes/Therapeutics

In the study, we aimed to compare the long-term impact of several diabetes screening strategies in China. Based on data from the China Health and Nutrition Survey and the published literature, we estimated model parameters and validated the model. We compared a set of screening strategies, including random screening for 50% of the population, and screening people who smoke, have unhealthy diet or have limited physical activity. Clinical trial designs were ascertained via the ClinicalTrials.gov website.

Results: Of 250 novel drugs approved by the FDA between 2011 and 2017, 11 (4.4%) were for antidiabetic indications. None of the 11 incorporated PROs in their labeling. However, 5 of the 11 (45.5%) collected QoL or treatment satisfaction data as a secondary or tertiary endpoint in at least 1 of the trials supporting approval. Measures included the EQ-5D, SF-36, and the Diabetes Treatment Satisfaction Questionnaire.

Conclusions: Although nearly half of all antidiabetic agents approved in the past 7 years assessed PROs during drug development, none acquired PRO label claims. As diabetes can have a significant impact on patients’ day-to-day functioning and QoL, failure to integrate PROs into labeling may represent a missed opportunity for patients, clinicians, and industry sponsors.
Use of a Machine Learning Algorithm Improves Prediction of Progression to Diabetes

AVIIT CAIN, AVI SHOSHAN, TAL SAGIV, RACHEL YESHIARIM, ITAMAR RAZ, RAN GOSHEN, JENNIFER CAI, MICHELLE HAN, MIKE INGHAM, MUKUL SINGHAL, HIANGKIAT (JASON) TAN, CRAIG I. COLEMAN, WILLIAM H. HERMAN, JENNIFER CAI, MICHELLE HAN, MIKE INGHAM, Wilmington, Delaware, DE; Storrs, Connecticut, CT; Jerusalem, Israel; Kfar Maccal, Israel

Identification a-priori of subjects at high risk of progression from prediabetes to diabetes may enable targeted delivery of interventional programs, while avoiding the burden of prevention and treatment in those at low risk. This study relies on the NIH THIN database cohort of 2,761,222 persons with at least 2 glucose measurements during an average follow-up of 6 years. Prediabetes was diagnosed in 470,107 persons, with 4.8% of them progressing annually to diabetes. We constructed a non-linear model identifying those at high risk of annual progression based on all available patient data and history. The major variables contributing to the model were glucose, HbA1c, BMI, age and gender. Using the clinically acceptable cutoffs of HbA1c≥6.0% and/or glucose≥10mmol/dl identified 76.5% of those who actually progressed to diabetes (sensitivity), while labelling 33.2% of the population as high risk (positivity rate). Setting our model at the same sensitivity yielded a lower positivity rate of 22.0%, thereby identifying the same number of progressors while labelling a significantly smaller population as high risk. The predictive ability of our model was superior to simple logistic regression based on glucose, HbA1c, BMI, age and gender as well (Table).

In conclusion, our algorithm enables judicious selection of the target population for a clinical intervention, with a higher positive predictive value, thus leading to cost saving.

| Table |
| Positivity rate | 33.2% |
| Positive predictive value | 10.9% |
| Specificity | 69.0% |

*All results are at a sensitivity point of 76.5%, the sensitivity of the cutoffs.*

Real-World Comparative Effectiveness, Treatment Patterns, and Costs in Type 2 Diabetes Mellitus (T2DM) Patients Initiated on Canagliflozin 300 mg (CANA) or a Glucagon-Like Peptide-1 Receptor Agonist (GLP-1)

MUKUL SINGHAL, HANGKIAT (JASON) TAN, CRAIG I. COLEMAN, WILLIAM H. HERMAN, JENNIFER CAI, MICHELLE HAN, MIKE INGHAM, Wilmington, Delaware, DE; Storrs, Connecticut, CT; Jerusalem, Israel; Kfar Maccal, Israel

This study compared HbA1c control, treatment patterns, and costs in adults with T2DM initiated on CANA or a GLP-1 based on administrative claims data from the HealthCare Integrated Research Database (4/2013-02/2016) augmented with laboratory data. The analysis included adult patients with ≥1 HbA1c result at baseline (BL) and in the 12-month follow-up period; statistical analysis was performed at 3-month intervals. Inverse probability of treatment weighting (IPTW) accounted for differences in baseline characteristics. From 12 months pre- to 12 months post-index (Figure), there were no significant differences in HbA1c at each 3-month interval in patients initiated on CANA (n = 750) vs. GLP-1 (n = 2417); results were consistent regardless of BL HbA1c (≥7%, ≥8%, or ≥9%) (data not shown). A greater proportion of patients were adherent to index medication (proportion of days covered ≥80%) over 12 months with CANA vs. GLP-1 (47.5% vs. 37.5%; P <0.001). The likelihood of discontinuation from index medication was lower with CANA than GLP-1 (49.6% vs. 57.4%; HR [95% CI]: 0.78 [0.70, 0.88]). Continuous 12-month pharmacy costs were $1,421 lower with CANA vs. GLP-1.

In summary, CANA initiation resulted in similar HbA1c values, greater adherence, less discontinuation, and lower treatment cost compared to GLP-1 in T2DM patients.

Key Clinical Risk Factors Identify Adverse Glycemia in Hospitalized Patients

MERYN KIY, JANE E. REID, ALEXANDRA GORELIK, SHANAL S. KUMAR, ANNA GALLIGAN, LOIS M. ROWAN, ALISON J. NANKERVIS, KATIE A. MARLEY, DAVID M. RUSSELL, PAUL R. WRAIGHT, PETER G. COLMAN, SPIROS FOURLANGIS, Melbourne, Australia

We previously showed that a proactive inpatient diabetes service decreased adverse glycemia (AG) and hospital acquired infections (RAP-IDS: ADA2017, 231-OR). To further focus our proactive care on high-risk inpatients, we investigated clinical risk factors associated with AG. We analyzed multiple clinical variables in 843 consecutive inpatients with diabetes or new hyperglycemia (random BG ≥11mmol/L). Capillary BG from day 2 of admission until discharge (censored at day 14) were analyzed. AG was defined as BG <4 or >15mmol/L on any day and recurrent AG (RAG) was defined as AG on ≥2 days. A split-sample multivariable logistic regression was performed with internal validation. The patient characteristics included 87% type 2 diabetes, 33% insulin-treated and mean HbA1c 7.6% AG and RAG occurred in 27/43% and 176/27% patients respectively. Pre-hospital factors (sulphonylurea or insulin treatment, HbA1c, Charlson index) and in-hospital factors (glycemia on day 1, length of stay) were independently associated with both AG and RAG (Table). Glucocorticoid treatment was associated with RAG but not AG. A model using these multiple variables accurately identified AG (ROC-AUC 0.88). Age, diabetes type, creatinine and admission unit were not associated with either AG or RAG. This study identified multiple key clinical risk factors associated with adverse glycemia, and may be used to better concentrate efforts for inpatient diabetes care.

| Table |
| Clinical variables associated with adverse glycemia & recurrent adverse glycemia: Glucocorticoid logistic regression |

In conclusion, our algorithm enables judicious selection of the target population for a clinical intervention, with a higher positive predictive value, thus leading to cost saving.
Physician-Targeted Education for Management of Chinese T2DM Patients Receiving Basal Insulin—BEYOND II Study Results

JIANPENG WENG, JIAJUN ZHAO, ZHIQIANG ZHOU, XIAOHUI GUO, XUEYING ZHENG, SHUI LUO, THE BEYOND II STUDY GROUP, Guangzhou, China, Jiangsu, China, Changsha, China, Beijing, China

BEYOND II was a multicenter, single-arm, observational study in which physicians received education based on T2DM treatment guidelines and effective patient education, reinforced by self-audit and peer-to-peer review over a 6-month period. The primary outcome measure was the proportion of study centers meeting individual improvement goals set by the Study Committee, based on HbA1c <7.0%. Two cohorts of ~100 patients (baseline cohort) were enrolled at each center. Of 71 centers that completed the study, 35 (49.3%) achieved improvement targets. Patients in the post-education cohort had improved glycemic control vs. the baseline cohort (Table). At centers meeting improvement targets, a higher proportion of physicians (n=156) self-rated as ‘confident in most cases’ about insulin initiation (89.9% vs. 78.9%), titration (87.4% vs. 80.9%), and hypoglycemia management (90.9% vs. 80.6%) post education vs. baseline, but there was no change at centers not meeting improvement targets. In a multivariate regression, completion of education (yes vs. no) had the strongest positive effect on initiation (89.9% vs. 78.9%), titration (87.4% vs. 80.9%), and hypoglycemia without confirmation (5.9% vs. 0.1%). Physician-targeted education was effective at around 50% of study centers for improving clinical outcomes and treatment strategies.

Table.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline cohort (N=6386)</th>
<th>Post-education P-value cohort (N=6353)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of centers meeting individual improvement targets, n(%), 95% CI</td>
<td>—</td>
<td>35/71 (49.3%; 97.2 to 61.4%)</td>
</tr>
<tr>
<td>Mean HbA1c, % (SD)</td>
<td>8.10 (1.732)</td>
<td>7.72 (1.579) &lt;0.001</td>
</tr>
<tr>
<td>Mean FPG, mmol/L (SD)</td>
<td>9.10 (3.580)</td>
<td>8.44 (3.172) &lt;0.001</td>
</tr>
<tr>
<td>HbA1c &lt;7%, % (n/N)</td>
<td>27.2 (1740/6386)</td>
<td>36.5 (2322/6353) &lt;0.001</td>
</tr>
<tr>
<td>FPG &lt;6.1 mmol/L, % (n/N)</td>
<td>15.6 (984/6386)</td>
<td>19.6 (1247/6353) &lt;0.001</td>
</tr>
<tr>
<td>Hypoglycemia (blood glucose ≤3.9 mmol/L or symptomatic hypoglycemia without confirmation), % (n/N)</td>
<td>4.4 (282/6386)</td>
<td>3.8 (241/6353) 0.077</td>
</tr>
</tbody>
</table>

Supported By: Sanofi
Because commonly used approaches may produce misleading results, consensus is needed.

**Table.** Performance of Logistic Regression Models to Predict All-Cause 30D Readmission.

<table>
<thead>
<tr>
<th>Performance Measurement</th>
<th>First Discharges without GEE</th>
<th>All Discharges without GEE</th>
<th>All Discharges with GEE</th>
<th>Area Under ROC Curve (C-statistic)</th>
<th>Correlation Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.921</td>
<td>0.871</td>
<td>0.803</td>
<td>0.075, 0.084</td>
<td>0.366, 0.403</td>
</tr>
</tbody>
</table>

**Model and Sampling Strategy**

**Brier Score 0.080**

**Correlation Coefficient 0.366**

Individualized Diabetes Risk Prediction in Women with a History of Gestational Diabetes

BERNICE MAN, ALAN SCHWARTZ, YINGLIN XIA, BEN S. GERBER, Chicago, IL

Without treatment, prediabetic women with a history of gestational diabetes (GDM) are 71% more likely to progress to type 2 diabetes (DM) compared to parous women without prior GDM. In women with prior GDM, both intensive lifestyle intervention (ILI) and metformin are effective in reducing the progression to DM in the Diabetes Prevention Program (DPP). Evidence suggests heterogeneity in treatment response.

We performed a secondary analysis of DPP data, including 1555 parous women with prediabetes; 19% had prior GDM, 31% were <45 years old, 44% were of non-Caucasian race/ethnicity and 71% were obese. At three years, 323 women developed diabetes. We examined 16 baseline clinical variables using Cox proportional hazards regression with backward elimination (excluding variables with p>0.05) to predict DM risk. Our final multivariable model includes treatment arm (ILI vs. metformin vs. placebo), BMI category, height, waist-hip ratio, fasting glucose and triglycerides, and hemoglobin A1c (Table). Interactions with treatment arms were explored.

This model differs from others recently developed for the general population, suggesting heterogeneity in treatment response. In the future, use of a clinical prediction model to calculate individual 3-year DM risk specifically for women with prior GDM would be useful in predicting treatment response. A347

Cost-Effectiveness Analysis of Empagliflozin Compared with Canagliflozin or Standard of Care (SoC) in Patients with T2DM and Established Cardiovascular (CV) Disease

ANURAG KANSAI, UDDETE REFSNIDER, JOSEPH LEE, KYLE FAHRBACH, PRANAV SANDE, EGINO FARI, ANASTASIA V. USTYUGOVA, Bethesda, MD, San Francisco, CA, Waltham, MA, Ridgefield, CT, Ingelheim, Germany

Empagliflozin, a sodium-glucose cotransporter 2 inhibitor, is FDA approved to reduce the risk of CV death in adults with T2DM and established CV disease. EMPA-REG OUTCOME showed a significant reduction in major adverse CV event (MACE), CV death, and hospitalization for heart failure (HHF) for empagliflozin vs. placebo in addition to SoC. Recently, CANVAS showed significant reduction in MACE and HHF with canagliflozin vs. placebo in addition to SoC. The objective of this study was to assess the cost-effectiveness of empagliflozin vs. canagliflozin or SoC in patients with T2DM and established CV disease in the U.S. A discrete event simulation model was used to simulate CV, renal, and select adverse events from EMPA-REG OUTCOME. Occurrence of each event was modeled using event-free survival curves with time-dependent covariates. A hazard ratio for canagliflozin vs. empagliflozin on each modeled event was estimated from published CANVAS data and EMPA-REG OUTCOME using an indirect treatment comparison. U.S. costs and utilities were taken from public sources. Patients receiving empagliflozin were predicted to live longer by 0.93 years vs. canagliflozin and 1.88 years vs. SoC due to lower CV death rates. When compared to SoC, empagliflozin had fewer or similar events per 100 patients-years, except for nonfatal stroke (NSTF) and genital mycotic infection (GMI). For empagliflozin vs. canagliflozin, there were less amputation (0.58 vs. 1.08), kidney injury (0.33 vs. 0.47), and bone fracture (1.12 vs. 1.45); similar nonfatal myocardial infarction (1.93 vs. 1.85), HHF (1.74 vs. 1.65), albuminuria progression (5.96 vs. 6.14), composite renal outcome (1.16 vs. 1.20), and GM (1.80 vs. 1.79); but more NSTF (2.20 vs. 0.85). Based on a $100,000/QALY threshold, empagliflozin was cost-effective compared with canagliflozin or SoC at $2,932/QALY or $35,489/QALY, respectively.

The Association of Glucose Values at Hospital Discharge with 30-Day Readmission and Post-discharge Mortality Rates in Patients with Diabetes

ELIAS SPANAKIS, GUILLERMO E. UMPIERREZ, MIN ZHAN, SOREN SNITKER, JEFFREY C. FINK, JOHN D. SORKIN, ELIAS SPANAKIS, GUILLERMO E. UMPIERREZ, TARIQ SIDDIQUI, MIN ZHAN, SOREN SNITKER, JEFFREY C. FINK, JOHN D. SORKIN, Baltimore, MD, Atlanta, GA

Objective: Thirty-day readmission and post-discharge mortality rates reflect quality of care. Little is known about the association of glucose values of the last day of hospital stay with the risk of readmission and mortality after discharge.

Design: Nationwide cohort of 836,189 admissions of DM patients admitted to non ICU setting in 110 Veteran Affairs hospitals, between 2000-2014. Demographic, social economic variables and several comorbidities were collected. General estimating equations were used to determine if the minimum glucose values of the last 24 hours of hospital stay were associated with 30-day readmission/mortality. Results: The 30-day readmission rate was 17.2% and the 30, 90 and 180-day mortality rates were 2.3%, 6.1% and 10% respectively, with a combined 18.8% for 30-day mortality/readmission rates. There was a sharp increase in the 30-day readmission rate with glucose values below 99 mg/dl. The post-discharge mortality rates increased with glucose values below 68.3 mg/dl, and the combined 30-day readmission/mortality rate increased with glucose values below 86.4 mg/dl (Figure).

Conclusions: DM patients with glucose values below 98 mg/dl and 68.3 mg/dl at the last day of hospitalization in the non ICU setting are at a higher risk for 30-day readmission and 180-day mortality.

Figure: Relative importance of glucose concentrations on 30-day mortality, readmission, and mortality or mortality. Color represents adjusted event rates; lines are 90% confidence intervals. Doses were stratified rates obtained by fitting the association of glucose concentration on non-Caucasian race and with a single tear weighing 150 mg/dl at the height.

Supported by: University of Illinois College of Medicine
Clinical Diabetes/Therapeutics

POSTERS

Economic Evaluation of Dapagliflozin as Add-On to Metformin in T2DM in the Israeli Health Care Setting

SHAI MOSHIEL, MICHAL HIRSCH VEXBERG, OREN SHAVIT, YOEL TOLEDANO, Tel Aviv, Israel

Background: Dapagliflozin is a potential for combination therapy with metformin in T2DM. However, its cost-effectiveness relative to other alternatives in the Israeli healthcare setup remains unknown.

Objective: To evaluate the cost-effectiveness of dapagliflozin 10mg as add-on to metformin, compared to common alternatives (sitagliptin 100mg, glimepiride 2mg, liraglutide 1.2mg) based on Meuhedet health services database.

Methods: A cost-effectiveness evaluation was performed using the Cardiff diabetes model. A cohort of 1000 T2DM patients (ages 21 and older) who had received additional medication to metformin was randomly chosen from Meuhedet’s database. Baseline values for demographic and clinical variables prior to the add-on therapy, along with data from clinical trials served as inputs to the model. Simulation was performed for each drug, calculating its total costs and benefits (QALYs). The model’s time horizon was set to 40 years, annual discount rate for both costs and benefits was 3.5% and incremental cost-effectiveness ratio (ICER) threshold was £20,000/QALY. Finally, single-variable and multivariable sensitivity analyses were performed.

Results: In the base-case scenario, dapagliflozin was found cost-effective compared to sitagliptin, liraglutide and glimepiride (ICER values of £1,232, £16,517 and £13,476, respectively). For all comparisons, ICER was driven by differences in costs, while differences in DALYs were minimal. Dapagliflozin remained cost-effective even after performing sensitivity analyses. However, when performing the simulation under comparators’ generic competition scenario, dapagliflozin was no longer cost-effective compared to liraglutide (ICER = £24,900/DALY).

Conclusion: Dapagliflozin as add-on treatment to metformin was cost-effective compared to several alternatives in T2DM patients in Israel’s healthcare system. Additional research is needed in order to evaluate the effects of evolving new clinical data.

Supported By: AmiaZeneca

Moderated Poster Discussion  ADA-Supported Research

1297-P

Regional Variations in Case Fatality following a Major Coronary or Cerebrovascular Event in People with Type 2 Diabetes—Evidence from the ADVANCE Trial and TECOS Trial

PHILIP M. CLARKE, XINYANG HUA, JOHN CHALMERS, MARK WOODWARD ESO., RUTH L. COLEMAN, JENNIFER B. GREEN, DARREN K. MCGUIRE, RURY R. HOLMAN, Melbourne, Australia, Sydney, Australia, Oxford, United Kingdom, Durham, NC, Dallas, TX

Objective: To explore possible differences in case fatality after a major coronary event (fatal or non-fatal MI, sudden death) or cerebrovascular event (fatal or non-fatal stroke) event in different regions of the world according to country’s geographical region and income level.

Method: We studied ADVANCE and TECOS participants who experienced a major coronary or cerebrovascular event during these two trials, with countries grouped by: 1) Geographical region; 2) World Bank income levels and examined all-cause mortality that occurred within 30 days after the event. We used logistic regression to derive odds ratios for fatal events, controlling for previous complications and for a range of clinical risk factors.

Results: Both studies showed that people from Asia and Central/Eastern Europe [compared with those from high income countries], had significantly higher odds of dying within 30 days after a major coronary event but not a major cerebrovascular event (Table). Conclusion: There are regional and income variations in all-cause mortality in people with type 2 diabetes following major coronary but not cerebrovascular events, which could be a result of disparities in emergency systems and MI treatments.

Table.

<table>
<thead>
<tr>
<th>Post major coronary event</th>
<th>Adjusted Odds Ratio (95% CI) for case fatality</th>
</tr>
</thead>
<tbody>
<tr>
<td>By geographic region</td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>3.13 (1.89-5.19)*** 3.82 (2.06-7.07)***</td>
</tr>
<tr>
<td>Central and Eastern EU</td>
<td>3.31 (2.00-5.49)*** 2.59 (1.54-4.33)***</td>
</tr>
<tr>
<td>By income group</td>
<td></td>
</tr>
<tr>
<td>Low and middle income countries</td>
<td>3.22 (2.13-4.88)*** 3.07 (1.95-4.83)***</td>
</tr>
</tbody>
</table>

1299-P

Outcomes of Telehealth in the Management of Type 2 Diabetes—A Systematic Review and Meta-analysis of Randomised Controlled Trials

NISHA NANGRANI, USMAN MALABU, VENKAT VANAGAVETI, Townsville, Australia, Douglas, Australia

Background: The outcomes of telehealth in the management of type 2 diabetes (T2DM) have not been evaluated since the publication of recent clinical trials.

Objective: To conduct a systematic review and meta-analysis of recently published randomized controlled trials (RCTs) to assess the biometric, clinical and psychosocial outcomes of telehealth in subjects with T2DM.

Methods: Electronic databases, MEDLINE, CINAHL, INFORMIT, SCOPUS and the Cochrane Central Register of Controlled Trials and reference lists of existing systematic reviews were searched until August 2017 to identify relevant studies. Study search and selection were performed by two independent reviewers. 4791 articles were retrieved of which 11 RCTs (n=5772) were included. A meta-analysis with random effects model was applied to estimate the pooled results.

Results: Telehealth was associated with a statistically significant and clinically relevant absolute decline in glycosylated haemoglobin (HbA1c) compared to usual care (mean difference -0.17%, 95% CI -0.25 to -0.09%, p<0.0001), especially if participants had a mean baseline HbA1c<8.0%; were less than sixty years of age or received telehealth for less than one year. There was no clinically significant reduction in LDL-cholesterol (LDL-c), body mass index (BMI), systolic (SBP) or diastolic blood pressure (DBP).

Conclusion: Telehealth interventions were associated with improved glycaemic control (HbA1c) in T2DM diabetic patients. However, no clinically relevant impact was observed on lipid profile, blood pressure, body mass index and psychosocial well-being. Future studies should seek to evaluate the effect of intervention duration on HbA1c, psychosocial outcomes and the effectiveness of telehealth in rural and underserved populations.

1296-P

1297-P

1298-P
A Population-Based Program Improving Diabetes Care

ALDO MARIOTTI, ARIELLA DE MONTE, FIRENZE, Italy

Objective: The aim of this study was to evaluate whether implementation of an integrated regional program can be effective in producing improvement in diabetes care.

Methods: Friuli Venezia Giulia is an Italian region accounting for about 1,250,000 population. A diabetic patients register based on administrative databases merging accounted in 2015 for a morbidity prevalence rate of 6.7%. Guidelines on diabetes integrated care were approved by the regional government. They were disseminated through a multifaceted intervention based on training, incentives to family physicians, primary care reorganization, modeling and proactive medicine. The program was assessed through the before-after intervention measure of process indicators. Analysis excluded gestational patients, those who didn’t consent for privacy reasons and those not included in the same family physician administrative list over the study period.

Results: Regionally, significant improvement in 2016 vs. 2015 was observed for all measures. Analysis included 54593 patients. The percentage of patients who received one ore more: A1c test arose from 73.8% in 2015 to 79.1% in 2016 (+7.2%), Microalbuminuria test arose from 44.7% in 2015 to 56.3% in 2016 (+21.6%), Blood Creatinine test arose from 70.3% in 2015 to 76.2% in 2016 (+7.8%), Lipid profile arose from 69.6% in 2015 to 72.6% in 2016 (+3.0%), Lipid profile arose from 42.1% in 2014-2015 to 47.9% in 2015-2016 (+13.8%). Hospital specific diabetes patients admission rate decreased from 342/1000 in 2015 to 328/1000 in 2016 (-4.2%). However, there was significant regional variation among all measures.

Conclusions: The evidence based introduction of an integrated professional and organizational intervention improved adherence to diabetes specific process measures in 2016 compared with 2015 baseline for patients assisted in Friuli Venezia Giulia region. A better integration with hospital care and a partial revision of IT system are needed.

HEALTH CARE DELIVERY—ECONOMICS/QUALITY IMPROVEMENT

Safe Ramadan Fasting Is Possible for Subjects with Poorly Controlled Type 2 Diabetes Mellitus

YING JIE CHEE, SHONDA NG, KEVIN J. KWEK, SHAIKH ABDUL KADER ABDUL SHAHID, Singapore, Singapore

Background: Poorly controlled diabetic patients (PCDP) are at increased risk during Ramadan fasting. International guidelines caution against Ramadan fasting among PCDP. However, many PCDP fast against medical advice. To our knowledge, no studies have specifically addressed the safety of Ramadan fasting by PCDP and hence, we aimed to study this.

Methods: Adults with type 2 DM attending a tertiary hospital’s Endocrinology clinic, who had fasted for at least 2 weeks in Ramadan, were evaluated. The safety and biochemical parameters were compared between the 2 groups based on pre-Ramadan glycemic control: Group 1 (HbA1c ≥ 9%) and group 2 (PCDP, HbA1c > 9%).

Results: We evaluated 139 Ramadan fasts by 113 participant-70 fasts were by PCDP, of which 26 were studied twice (2016 and 2017). The results are summarised below.

Hypoglycemia was more frequent in group 1 compared to PCDP (p = 0.017). However, there was no significance in other safety parameters between both groups. None of the PCDP suffered from hyperglycemia that needed to break fast.

Conclusion: Most of the PCDP in our cohort were able to fast safely during Ramadan. Our findings need to be confirmed with prospective studies in different ethnic and geographic settings. PCDP with no prior hyperglycemic crisis can fast during Ramadan safely if specific education is offered and may even harness the beneficial effects of Ramadan such as metabolic memory.

Table.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1 (N=69; mean HbA1c 7.8%)</th>
<th>Group 2 (N=70; mean HbA1c 10.8%).</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of days fasted (Mean)</td>
<td>26.9</td>
<td>27.1</td>
</tr>
<tr>
<td>Polydipsia (N)</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>Hypoglycemia (N)</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>Hypoglycemia (capillary blood glucose &lt; 5 mmol/L, N)</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Need to break fast due to hypoglycemia (N)</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>Need to break fast due to hyperglycemia (N)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mean HbA1c change (%), pre and post-Ramadan</td>
<td>+0.18</td>
<td>-0.28</td>
</tr>
</tbody>
</table>

Awareness of Preconception Care for Women with Type 1 Diabetes—From Family Members’ Perspective

CHAOAN WANG, SHUJU LIU, XIUYING ZHENG, XILING HU, JINHUA YAN, YAN GUI, SHANSHAN XIUING, DAIZHI YANG, LILING QIU, BIN YAO, JIANPING WENG, Guangzhou, China, ZHONGSHAN, China

Background: Preconception care (PCC) can improve pregnancy outcomes in women with type 1 diabetes (T1D). Little was known on current status of PCC in China. We aimed to investigate the current practice and attitude about PCC from the perspective of the patients’ family members.

Method: We conducted in-depth interviews with family members of T1D women. By purposive sampling we included their husbands, parents and parents-in-law. Transcripts of the interviews were coded into themes by 3 researchers via thematic framework method and analyzed in NVIVO 11. The recruitment ended when no new themes emerged.

Results: We interviewed 16 family members of 14 T1D women (10 husbands, 4 mothers, 1 father and 1 mother-in-law) and rendered 9 themes. 1) Knowledge of T1D and PCC: most demonstrated little knowledge of both due to lack of education. 2) Content of PCC: dietary guidance and glycemic control were most required. 3) Timing of starting PCC: adulthood was most recommended while the rest adolescence. 4) Approach of PCC: internet and on-site consultation were well recognized while tutorials and materials as supplements. 5) Multi-disciplinary cooperation: most suggested that endocrinology professionals take the main responsibility of PCC with other professionals. 6) Attitude on pregnancy: most thought women had the obligation of childbearing while the rest showed respect to the women’s own decision. 7) Concern: worries on complications during pregnancy, inheritance of T1D, social discrimination and economic cost. 8) Doctor-patient communication: most considered the information and consultation time provided by doctors were inadequate. 9.) Peer support: peer communication was mainly supported in order to convey experience and confidence while the minority opposed it fearing the spread of negative information.

Conclusions: Family members of T1D women scarcely owned knowledge of PCC and suffered various concerns. Their participation in PCC should be encouraged and mental support should be enhanced.

Supported By: National Health and Family Planning Commission (201502011); World Diabetes Foundation (WD14-921) Sun Yat-sen University (2007030).

1301-P

A349
We have mandatory insulin pump orders for inpatients. To determine the timing of CSII orders, documentation and glucose levels, we performed a retrospective review of patients admitted from the ED who remained on CSII, from June 2012 to August 2016.

32 patients (age 54.3 ± 14.6 years) were admitted to the hospital from the ED who were continued on CSII. We were unable to capture data on ED patients not admitted or who had their CSII discontinued. 37.5% did not have CSII orders written within 12 hours of presentation to the ED. The average time to insulin pump order was 13.3 hours. 43% presented to the ED between 1900-0700. The mean time to first glucose was 1.27 hours ± 1.47, and 15.6% had no glucose check within the first 2 hours. <50% had HbA1c integrity documented (insulin reservoir, site intact, battery capacity) in the first 24 hours. Glycemic control was assessed by 6-hour periods. For these 4 periods: Glucose >180 mg/dl (13/32; 12/32; 12/32; 12/32; >180 mg/dl (18/32; 11/32; 12/32; 12/32; >80 mg/dl (6/32; 2/32; 2/32; 2/32); no glucose (0/32; 3/32; 3/32; 3/32). Continuous glucose monitor readings are not part of the patient’s medical record as not approved for clinical decision making.

We found few patients had CSII orders or documentation nor appropriate glucose monitoring in the initial 12 hours after presentation to the ED. We anticipate new ED policies, procedures, and RN protocols, with use of new ED pump order sets and early patient involvement, will improve guideline compliance and patient care.

1305-P

HbA1c Screening Characterizes Undiagnosed Dysglycemia in Surgical Patients

We have mandatory insulin pump orders for inpatients, however, and administration is accurate and safe. However, if the pen is used on more than one patient, there is potential risk of infection with pathogens including hepatitis viruses and HIV. Rapid-acting insulin (RAI) is a time-critical medication, both for correction and nutritional doses. Many hospitals using insulin pens choose to dispense them with a patient specific ID barcode from the pharmacy. This workflow ensures the correct patient ID for scanning, yet it may result in dispensing duplicates and may create time-critical delays. At UCSF, automated dispensing machines (ADM) on adult-units house time-critical medications, including RAI. In this workflow, the RN labels the insulin pen with the patient specific 3D barcode generated on the unit. Prior to insulin pen administration, 3 barcodes must be scanned: 1. Patient armband, 2. Patient label on insulin pen, (NEW) 3. Insulin pen manufacturer (confirms an active order for this type of insulin). The EMR will flash a screen size alert with a red stop sign and a warning if the patient’s armband ID and the pen’s label patient ID do not match. Implemented in 2/2017, this workflow and alert system, for the approximately 18,000 insulin pen SQ administrations per month has triggered 10-25 alerts per month. As of 11/1/2017, all alerts have stopped the process and the correct patient’s insulin pen was retrieved and administered. Each alert is followed by an investigation. Significant factors contributing to the triggering of an alert involve RNs caring for >1 patient with RAI insulin orders, pens returned to the wrong patient specific cardiac care unit in centralized medication rooms, carrying > 1 patient’s insulin pen at a time and opening > 1 patient’s EMR in the patient’s room when scanning. We conclude that pen misuse can be avoided with compliance to our triple scanning system, in conjunction with best practices, while preserving the critical timing of rapid-acting insulin.

1306-P

The Pre-Diab Perioperative Study—A Structured Perioperative Diabetes Management Plan Improves Medication Usage and Glycemia in Elective Surgery
QI YANG, DAMIEN QI, ELIZABETH J. PEMBERTON, MERVYN KI, PETER G. COLMAN, SPIROS FOURLANOS, Melbourne, Australia

The perioperative management of diabetes inpatients is complex, often inconsistent and frequently results in suboptimal glycaemia. We designed, implemented and evaluated a structured perioperative diabetes management plan (PDMP) on appropriate diabetes medication usage and glycaemia in the perioperative period, in elective non-cardiac surgery patients. A multidisciplinary team developed and implemented a novel structured PDMP at our tertiary hospital. This observational study audited perioperative diabetes management over 4 months pre-implementation (non-structured care) and 4 months post-implementation (structured PDMP care). Primary outcome was appropriate use (documented recommendation, prescription and administration of diabetes medications). Secondary outcomes included blood glucose (BG) monitoring practice and glycaemia. Pre- and post-implementation groups comprised 138 and 141 patients respectively, all of whom attended preadmission clinic and were admitted on the day of the procedure. The two groups were well matched in clinical characteristics. The PDMP was completed correctly in 107 (76%) patients in the post-implementation group. The appropriate use of diabetes medications increased from 30% to 72% between pre- and post-implementation groups (p<0.001). Appropriate BG monitoring also increased (26% vs. 51%, p<0.001). There was improvement in glycaemia with post-implementation group having lower BG in the perioperative period (10.3±4.6 vs. 9.0±3.8 mmol/L, p<0.001); postoperative period (10.4±3.5 vs. 9.3±3.6 mmol/L, p=0.002); and in the entire perioperative period (10.3±4.1 vs. 9.0±3.8 mmol/L, p<0.001). This practical, implementable and novel structured perioperative diabetes management plan for elective surgery patients significantly improved diabetes medication usage, BG monitoring, and glycaemia in the perioperative period.

1307-P

Improving the Recognition and Management of Elevated Blood Pressure among Youth with Type 1 Diabetes
KAJAL GANDHI, DON A. BUCKINGHAM, JR., JESSICA HEMIYER, ALYSSA M. KRÄMER, KATHRYN OBYNBA, JUSTIN A. INDIK, MANMOHAN K. KAMBOJ, Columbus, OH

Background. Studies show that youth with type 1 diabetes (T1D) harbor cardiovascular risk factors and exhibit clinical signs suggestive of cardiovascular disease. ADA and ISPAD guidelines promote regular blood pressure screening to reduce cardiovascular risk, and strategies should involve effective screening and management. The diabetes clinic previously had limited measures in place to manage T1D youth with elevated blood pressure.

Objective. The aim of this quality improvement (QI) project was to increase provider recognition and follow-up of T1D patients with elevated blood pressure readings ≥ 95thile for age/height, from 0% to 50%, by 12/31/17 and sustain through 12/31/2018.

Methods: After the QI team clarified project goals, a Key Driver Diagram (KDD) and elevated blood pressure process map was developed. This algorithm aided to clarify the care process to efficiently recognize and manage youth with T1D who presented with elevated blood pressure in the outpa
Patient-Centered Outcomes of a Randomized Trial of Blood Glucose Monitoring Technology and Family-Centered Goal Setting

JILLIAN B. HALPER, TAMARA HANNON, USA YAZEL-SMITH, Indianapolis, IN

Adequate frequency of self-monitoring of blood glucose (SMBG) is important to maintain glycemic control. Real-time sharing of adolescent SMBG data with parents and providers is possible, however, adolescents may be reluctant to adopt this technology. The objective of this research was to determine patient-centered outcomes of adolescent-parent research participant pairs who were randomized to utilize: 1) a glucometer that shared blood glucose data among patients, parent, and providers, and allowed for communication; 2) family-centered goal setting; and 3) a combination of 1 and 2. We evaluated data from 97 adolescent-parent pairs in the form of 10 validated surveys; we modeled longitudinal changes in survey responses from baseline to 6 months. Differences between treatment groups were evaluated using ANOVAs and changes within patients over time were evaluated using paired t-tests. Patient and parent satisfaction was high at the onset of the intervention: 4.31 out of 5 and 4.55 out of 5, respectively. Parent Satisfaction Survey (p = 0.04) and Parental Environment Questionnaire (p = 0.006) results decreased over time; there was no significant change for any other surveys. Our data suggest that it is important to individualize therapy to meet patient-centered goals and acknowledge this when designing interventions to improve health outcomes in adolescents with T1D.

Incorporating Depression Screening into Diabetes Clinics across the T1DX Learning Collaborative


Objective: Depression contributes to suboptimal health outcomes of community healthcare delivery. We managed to build a digital healthcare ecosystem that engages diabetic patients and pharmacists with a cloud engine that operates in the healthcare ecosystem with retail pharmacists as the care provider. This project builds on comprehensive diabetes care, with the hope of reducing future cardiovascular burden for youth with T1D.

Does Initiation of Basal Insulin Analogs in Patients with Type 2 Diabetes Mellitus Confer Advantages over Neutral Protamine Hagedorn (NPH) for Severe Hypoglycemia and Glycemic Control?

KASIA J. LIPSKA, MELISSA M. PARKER, HOWARD H. MOFFET, ELBERT HUANG, ANDREW J. KARTER, New Haven, CT, Oakland, CA, Chicago, IL

In clinical trial populations, long-acting insulin analogs modestly reduce the risk of nocturnal hypoglycemia compared with neutral protamine Hagedorn (NPH) in type 2 diabetes, but cost 2-4 times more. In real-world clinical practice, insulin performance may vary due to greater heterogeneity of patient characteristics and behaviors.
To compare rates of severe hypoglycemia and changes in glycemic control associated with insulin analogs vs. NPH, we conducted a propensity-score matched cohort analysis using data from Kaiser Permanente Northern California (2006 to 2015). We included patients with type 2 diabetes if they started a long-acting insulin analog or NPH, and we censored follow-up at death, loss of health plan coverage, change in type of insulin used, change in sulfonfonyurea treatment, or end of follow-up. Main outcomes were time to hypoglycemia-related utilization (emergency department visit or hospitalization with a primary or principal discharge diagnosis of hypoglycemia) and change in hemoglobin A1c within 1 year of insulin initiation. Among 1,928 patients with type 2 diabetes who started insulin analogs and 23,561 who started NPH, there were 31 and 319 hypoglycemic events, respectively. After propensity score matching, the hazard ratio for severe hypoglycemia associated with insulin analog use was 0.95 (95% CI, 0.57, 1.6) and did not change significantly after additional adjustment for prior severe hypoglycemia and time-dependent diabetes medication use (HR 0.97, 95% CI 0.58, 1.54). Hemoglobin A1c decreased from 9.4% to 8.1% after initiation of insulin analogs and from 9.4% to 7.9% after initiation of NPH (difference-in-difference -0.19% (95% CI, -0.06, -0.34%)).

In real-world clinical practice, the use of basal insulin analogs is not associated with a substantial reduction in hypoglycemia-related utilization or improvement in glycemic control compared with NPH insulin.

Supported By: National Institutes of Health

Health Care Delivery—Economics/Quality Improvement

1312-P
Managing Diabetic Patients with Hypertension Comorbidty by Retail Pharmacists Using a Digital Solution in China

WEI WANG, YINGJIE LI, ZHEN WANG, DONGXING LI, HONGGUANG ZHANG, KAI LIU, JIUMEI CAO, WEI WANG, ZHEN WANG, KAI LIU, JIUMEI CAO, Shanghai, China

Objective: To identify the effects of implementing a digital approach at pharmacies to manage the healthcare outcomes of comorbidities of diabetes and hypertension.

Methods: A digital solution that includes a set of blood glucose (BG) and blood pressure (BP) tele-monitors, an App, and a cloud engine with decision support algorithms was implemented in 941 drug stores in 91 cities in China. During Jun 8th 2015 to Dec 26th 2017, a total of 3,468 patients of both uncontrolled BG and BP were recruited to receive the monthly in-store healthcare services of: 1) BG and BP testing with the results synchronized to the cloud, 2) App-assisted lifestyle modification for meal planning, coaching and exercise, and 3) App-guided medication consultation.

Results: The study population had an average age of 65.3 ± 10.1, BMI of 24.6 ± 3.3, and male of 47.2%. Their fasting blood glucose (FBG) and random blood glucose (RBG) were reduced by 0.8 mM (baseline: 9.1 ± 2.2 mM, last time: 8.3 ± 2.3 mM, P = 0.001) and 3.1 mM (baseline: 14.4 ± 3.2 mM, last time: 11.3 ± 4.0 mM, P = 0.001), respectively. Systolic and diastolic BPs were reduced by 9.1 mm Hg (baseline: 174.6 ± 17.4 mm Hg, last time: 165.2 ± 18.7 mm Hg, P = 0.001) and 4.4 mm Hg (baseline: 86.5 ± 11.1 mm Hg, last time: 82.1 ± 11.6 mm Hg, P = 0.001), respectively. The proportion of controlled diabetic and hypertensive patients was 30.0% (n = 1004, P = 0.001) and 38.1% (n = 1251, P = 0.001) by the time of this analysis. Patients were satisfied with the intervention due to the convenient access to the digital database and the services available. The health outcomes were not associated with geographic differences or economic status of the site.

Conclusion: Mobilizing community pharmacists with new digital technologies presents an effective approach to provide patient-centered care for diabetic patients with comorbidities such as hypertension.

Supported By: National Institutes of Health

1313-P
Application of a Cloud-Based Medication Adherence Improvement (MAI) System to Assist Diabetic Care in China

YINGJIE LI, JIUMEI CAO, WEI WANG, ZHEN WANG, DONGXING LI, HONGGUANG ZHANG, KAI LIU, Shanghai, China

Objective: To evaluate the effects on medication adherence by implementing a cloud-based medication adherence improvement system to assist diabetic care in China.

Methods: Data was collected through retrospective chart review of all patients in the Shanghai Medical Center from April 2015 through June 2015. A successful transition was defined as one in which the insulin drip was not restarted, mean blood glucose (RBG) were reduced by 0.8 mM (baseline: 9.1 ± 2.2 mM, last time: 8.3 ± 2.3 mM, P = 0.001) and 3.1 mM (baseline: 14.4 ± 3.2 mM, last time: 11.3 ± 4.0 mM, P = 0.001), respectively. Systolic and diastolic BPs were reduced by 9.1 mm Hg (baseline: 174.6 ± 17.4 mm Hg, last time: 165.2 ± 18.7 mm Hg, P = 0.001) and 4.4 mm Hg (baseline: 86.5 ± 11.1 mm Hg, last time: 82.1 ± 11.6 mm Hg, P = 0.001), respectively. The proportion of controlled diabetic and hypertensive patients was 30.0% (n = 1004, P = 0.001) and 38.1% (n = 1251, P = 0.001) by the time of this analysis. Patients were satisfied with the intervention due to the convenient access to the digital database and the services available. The health outcomes were not associated with geographic differences or economic status of the site.

Conclusion: Text message-based knowledge delivery is an effective way to improve medication adherence for community diabetic patients.

1314-P
Economic Evaluation of Dapagliflozin vs. Other Oral Hypoglycemic Drugs in China via Idealized Model

JIANG ZHENG, LU LONG, ZI YE, LULU CHEN, Wuhan, China, Shanghai, China

Objective: To evaluate the effects on medication adherence by implementing a digital approach at pharmacies to manage the healthcare outcomes of comorbidities of diabetes and hypertension.

Methods: A digital solution that includes a set of blood glucose (BG) and blood pressure (BP) tele-monitors, an App, and a cloud engine with decision support algorithms was implemented in 941 drug stores in 91 cities in China. During Jun 8th 2015 to Dec 26th 2017, a total of 3,468 patients of both uncontrolled BG and BP were recruited to receive the monthly in-store healthcare services of: 1) BG and BP testing with the results synchronized to the cloud, 2) App-assisted lifestyle modification for meal planning, coaching and exercise, and 3) App-guided medication consultation.

Results: The study population had an average age of 65.3 ± 10.1, BMI of 24.6 ± 3.3, and male of 47.2%. Their fasting blood glucose (FBG) and random blood glucose (RBG) were reduced by 0.8 mM (baseline: 9.1 ± 2.2 mM, last time: 8.3 ± 2.3 mM, P = 0.001) and 3.1 mM (baseline: 14.4 ± 3.2 mM, last time: 11.3 ± 4.0 mM, P = 0.001), respectively. Systolic and diastolic BPs were reduced by 9.1 mm Hg (baseline: 174.6 ± 17.4 mm Hg, last time: 165.2 ± 18.7 mm Hg, P = 0.001) and 4.4 mm Hg (baseline: 86.5 ± 11.1 mm Hg, last time: 82.1 ± 11.6 mm Hg, P = 0.001), respectively. The proportion of controlled diabetic and hypertensive patients was 30.0% (n = 1004, P = 0.001) and 38.1% (n = 1251, P = 0.001) by the time of this analysis. Patients were satisfied with the intervention due to the convenient access to the digital database and the services available. The health outcomes were not associated with geographic differences or economic status of the site.

Conclusion: Mobilizing community pharmacists with new digital technologies presents an effective approach to provide patient-centered care for diabetic patients with comorbidities such as hypertension.

Supported By: National Institutes of Health

1314-P
An Assessment of Protocol Utilization and Efficacy when Transitioning from Infusion to Subcutaneous Insulin at an Academic Medical Center

LAUREN VINCENT, KEVIN BOX, KRISTEN KULASA, San Diego, CA

Background: The transition from intravenous to subcutaneous insulin is a complicated process often associated with poor glycemic control. Our academic medical center has protocols for guiding providers through this transition. Our protocols have previously been shown to improve glycemic control. We sought to assess protocol utilization and whether it continues to produce successful insulin transitions.

Methods: Data was collected through retrospective chart review of all transitions from intravenous to subcutaneous insulin completed at our medical center from April 2015 through June 2015. A successful transition was defined as one in which the insulin drip was not restarted, mean blood glucose was less than 180 mg/dL for the first 48 hours after transition, and there was no hypoglycemia (blood glucose less than 70 mg/dL).

Results: Compared with other oral hypoglycemic drugs, the application of dapagliflozin allows each type 2 diabetic patient to save an average of 14279.57 CNY on cardiovascular events annually in China. The annual per capita treatment cost for patients receiving dapagliflozin in the control of blood glucose and cardiovascular events was 66.98% of that of patients in the first and second-line treatment regimens, and was 65.83% of that of patients in the second-line treatment regimen.

Conclusions: Based on this idealized model, dapagliflozin is expected to save 33.10% of annual cost on glycemia control and cardiovascular complications in patients with type 2 diabetes compared to patients treated with the first and second-line treatment regimens and to save 34.17% of annual cost compared to patients treated with the second-line treatment regimen in China.

Supported By: AstraZeneca China
Predictors of Achieving Glycemic Targets among People with Type 2 Diabetes—The CARRS Trial


While poor glycemic (A1C), blood pressure (BP), and lipid control are common in patients with diabetes, the CARRS Trial among 1,148 type 2 diabetes patients showed the effectiveness of a multi-component intervention (care coordinators and decision-support electronic health records). Compared to usual care, the intervention was associated with twice the probability of achieving glycemic and combined diabetes care goals (A1C<7% and BP<130/80 mmHg or LDL<100 mg/dL). In absolute terms, however, only 20% of the intervention participants achieved glycemic targets. In this analysis, we evaluated the predictors of achieving good (A1C<7%) and avoiding poor glycemic control (A1C>9%) among CARRS participants (mean age: 54.2 years, median diabetes duration: 7 years, and mean A1C: 9%). Using generalized estimating equations, we analyzed four regression models (demographics, disease-related, self-care and other risk factors) to identify predictors of glycemic control, adjusting for intervention. We found income, education, diabetes duration, adherence to prescribed medication/diet/exercise, and diabetic retinopathy to be significantly associated with glycemic control, adjusting for intervention. We highlight the importance of tailoring interventions based on socioeconomic status (SES) and disease characteristics and also further research into innovations to facilitate better self-care in lower SES groups.

Table 1: Factors associated with achieving glycemic targets

<table>
<thead>
<tr>
<th>Factors</th>
<th>A1C &lt; 7%</th>
<th>A1C ≥ 7%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Income (US$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15,000</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>15,000-20,000</td>
<td>1.01 (1.02, 1.41)</td>
<td>0.97 (0.94, 1.01)</td>
</tr>
<tr>
<td>20,000-35,000</td>
<td>1.10 (0.97, 1.25)</td>
<td>0.99 (0.95, 1.04)</td>
</tr>
<tr>
<td>≤35,000</td>
<td>0.99 (0.85, 1.15)</td>
<td>0.95 (0.90, 1.00)</td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up to primary school</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>Secondary school</td>
<td>1.21 (0.92, 1.61)</td>
<td>1.04 (0.86, 1.25)</td>
</tr>
<tr>
<td>Graduate or above</td>
<td>1.25 (1.17, 1.34)</td>
<td>1.25 (1.10, 1.42)</td>
</tr>
<tr>
<td>Diabetes duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 years or less</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>6-10 years</td>
<td>1.00 (0.85, 1.18)</td>
<td>1.00 (0.85, 1.18)</td>
</tr>
<tr>
<td>11-15 years</td>
<td>1.02 (0.86, 1.21)</td>
<td>1.01 (0.85, 1.20)</td>
</tr>
<tr>
<td>&gt;15 years</td>
<td>1.42 (1.02, 1.97)</td>
<td>1.42 (1.02, 1.97)</td>
</tr>
<tr>
<td>Adherence to prescribed medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Adherent</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Adherent</td>
<td>1.35 (1.02, 1.80)</td>
<td>1.35 (1.02, 1.80)</td>
</tr>
<tr>
<td>Adherence to diet plan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Adherent</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Adherent</td>
<td>1.79 (1.47, 2.19)</td>
<td>1.79 (1.47, 2.19)</td>
</tr>
<tr>
<td>Adherence to exercise plan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Adherent</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Adherent</td>
<td>1.07 (0.88, 1.30)</td>
<td>1.07 (0.88, 1.30)</td>
</tr>
</tbody>
</table>

**Table 1.** Factors associated with achieving glycemic targets

**Table 2.** T1D Staff FTE to Patient Ratios of Pediatric vs. Adult Diabetes Clinics in the T1D Exchange

<table>
<thead>
<tr>
<th>Staff Type</th>
<th>Pediatric</th>
<th>Adult</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician</td>
<td>1.171</td>
<td>1.33</td>
<td>0.63</td>
</tr>
<tr>
<td>Nurse Practitioner</td>
<td>1.347</td>
<td>1.647</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Certified Diabetes Educator</td>
<td>1.58</td>
<td>1.19</td>
<td>0.57 &lt;0.001</td>
</tr>
<tr>
<td>Registered Dietician</td>
<td>1.379</td>
<td>1.797</td>
<td>0.133 &lt;0.001</td>
</tr>
</tbody>
</table>

**Table 2.** T1D Staff FTE to Patient Ratios of Pediatric vs. Adult Diabetes Clinics in the T1D Exchange

**Table 2.** T1D Staff FTE to Patient Ratios of Pediatric vs. Adult Diabetes Clinics in the T1D Exchange
Clinical Diabetes/Therapeutics

1319-P

EXSCEL—Once-Weekly Exenatide Reduces Medical Resource Utilization in Patients with Type 2 Diabetes Mellitus
SHELBY D. REED, YANHONG LI, HELEN A. DAKIN, FRAULIE BECKER, JOSE LEAL, STEPHANIE GUSTAVSON, BERNT KARTMANN, ERIC T. WITBRODT, ROBERT J. MENTZ, NEHA PAGDIPATI, M. ANGELINA BETHEL, ALASTAIR M. GRAV, RUBY R. HSILMAN, ADRIAN F. HERNANDEZ, DURHAM, NC, OXFORD, UNITED KINGDOM, GAITHERSBURG, MD, MOLNDAL, SWEDEN, WILMINGTON, DE

Objectives: To evaluate the effect of exenatide 2mg once-weekly vs. placebo in addition to usual care on medical resource use among 14,572 patients with type 2 diabetes enrolled in the Exenatide Study of Cardiovascular Event Lowering (EXSCEL), which demonstrated a statistically non-significant reduction in major adverse cardiovascular events and a nominally significant reduction in all-cause mortality with exenatide once-weekly administration.

Methods: Data on medical resource use were collected from randomization to study end. Hierarchical generalized linear models were used to compare medical resource use between groups, with an offset to account for patient-level of follow-up duration. Random intercepts modeled country-specific variations in resource use and a fixed effect modeled the relative impact of exenatide vs. placebo.

Results: Mean follow-up was 3.3 years in both groups. The mean number of hospitalizations was similar between the two groups (0.83 in the exenatide group vs. 0.84 in the placebo group; p=0.31), as were annual hospitalization rates, ranging from 0.20–0.29 per person-year from Year 1 to Year 5. The mean cumulative number of inpatient days over the trial follow-up period was 0.41 days lower in the exenatide group than in the placebo group (7.05 days vs. 7.46 days, respectively; relative rate ratio: 0.910; p=0.048). Patients treated with exenatide had an average of 6.88 outpatient visits to usual diabetes care providers compared to 9.14 for patients treated with placebo (p=0.048). Outpatient visits to other healthcare providers were similar at 12.19 for the exenatide group vs. 11.78 for the placebo group (p=0.80).

Country-level variations in resource use were significant.

Conclusions: Type 2 diabetes patients treated with exenatide in addition to usual care incurred significant reductions in inpatient hospital days and outpatient visits to their diabetes care providers compared to patients treated with placebo in addition to usual care.

1320-P

Implementation Strategy for a Digital Health Tool Influences User Engagement
MANSUR SHOMALI, MALINDA PEEPLES, BALTIMORE, MD, COLUMBIA, MD

Background and Aims: Digital health tools not only should be effective in clinical trials, but should be implemented into the healthcare ecosystem without adding undue burden for the patient and the care team. We hypothesized that different modes of implementation may be associated with differences in engagement.

Method: In the first model, users received a prescription for a FDA-cleared digital tool from their healthcare providers. In the second model, certified diabetes educators provided the digital tool to their patients. In the third model, the digital tool was distributed via a direct-to-patient email from a large, national health plan for Medicare enrollees. The user data was collected electronically and de-identified according to data policies.

Results: 3,141 users were identified as part of the provider prescription model. Of note, 30.7% of users did not enter their diabetes medications into the system. 136 users were identified in the educator-driven model. Again, a significant minority (25.3%) did not enter their diabetes medications. In the health plan model, of the 11,000 enrollees who were invited to participate by email, 161 individuals activated accounts. Interestingly 67% of these users engaged with the digital tool via the web, not on mobile devices.

Conclusions: In the provider prescription and the educator models, individuals were provided the digital tool during a face-to-face visits. Though overall engagement with the system was good, a significant minority of users still did not enter their medications into the system. In the health plan driven model, only a small proportion of recipients of the emails activated their accounts. Surprisingly, those users were more likely to use the web portal vs. the mobile app. These insights can be used to guide the effective integration of digital tools into clinical practice.

1321-P

Establishment of the Type 1 Diabetes Exchange QI Learning Collaborative (T1DX-LC)

Background: The proportion of patients with type 1 diabetes (T1D) who meet recommended HbA1c targets remains suboptimal, with little improvement over the last two decades. A Learning Collaborative (LC) is a multi-clinic learning and sharing quality improvement (QI) process known to accelerate improvement in chronic conditions. We created the T1DX-LC to spread learning to improve health outcomes of individuals living with T1D.

Methods: In 2014, a design process engaged clinicians, researchers, patient advocates, and QI leaders to develop a roadmap for improvement, based on the Chronic Care Model. The T1DX-LC launched in 2016 with 7 pediatric and 3 adult diabetes practices, coordinated by the T1D Exchange (BOSTON, MA). Over 18 months, we established a LC foundation: teams representing each clinic, governance, QI training and capability, online collaboration space, standard measures, and population data systems. Teams selected clinical tests of change for pilot for depression screening, pre-visit planning, and patient-centered clinic design.

Results: Teams completed formal QI coursework and collaborated via monthly calls, emails, an online collaboration space, and 3-person learning sessions. Six teams increased depression screening, 5 teams adopted multiple change ideas for pre-visit planning, and 5 teams shared patient-centered tools and practices. A QI capability assessment survey was established and showed proficiency for all teams. We established a HIPAA-compliant data repository, data formatting specifications, data extraction/transmission standards, and a prototype data visualization dashboard. Two sites demonstrated the ability to extract and transmit EHR data to the central database.

Conclusions: The T1DX-LC demonstrated broad engagement, improved QI capability, advanced 3 focus areas, and developed a data exchange infrastructure. Our next steps are to build upon these efforts to accelerate improvement of outcomes in high-risk patients with T1D defined by HbA1c>9%.

Supported By: The Leona M. and Harry B. Helmsley Charitable Trust

1322-P

An Innovative Cost-Effective Model of Using Advanced Care Practitioners (ACP) in Improving Glycemic Control and LOS in a Large Hospital System
RENU JOSHI, AMY HELMUTH, MECHANICSBURG, PA, HARRISBURG, PA

In 2001 healthcare systems identified issues related to increased length of stay and suboptimal outcomes associated with poor patient glycemic control. Diabetes clinical initiative (DCI) team was created and the physician champion developed protocols and restructured the delivery of diabetic care across the healthcare system. However it was difficult to provide uninterrupted service due to shortage of Endocrinologists.

An innovative care model was designed in 2009 using specialty trained Endocrinology ACPs to improve Glycemic control across system and to provide uninterrupted service including weekends. The ACP’s were trained by the physician champion both with didactic teachings and ongoing case discussions. Automatic consults to ACPs’ were initiated for specific criteria identified by lead physicians. These criteria included: blood glucose (BG) greater than 200 X4 in 24 hours, BG greater than 300 X2 in 24 hours and Hypoglycemia less than 40 X2 in 24 hours. The ACP’s were always supported by the endocrinology team.

For the last 8 years the glycemic control across the hospital has further improved from average blood glucose of 160-153mg/dl. The rate of mild hypoglycemia remains low at 2% and severe hypoglycemia at < 0.4%. This has resulted in continuation of improved LOS and patient satisfaction as well. Much improved results in Coronary artery bypass surgery (CABG) population have been shown with no deep sternal wound infections in last 6 years. The model remains cost effective for the whole system.

Summary: Innovative model of Glycemic control using specialty trained ACPs is cost effective and improves glycemic control and LOS. The ongoing education and support is critical to the success of the program.
Development of a Clinical Screening Tool for Undiagnosed Diabetes in a Hospital Observation Unit


Background: While diabetes mellitus (DM) is typically diagnosed in the outpatient setting, 30% of patients in the U.S.A remain undiagnosed, prompting novel approaches to screening. There are 2 million Observation Unit (OU) stays annually in the U.S.A. The OU allows prolonged care for Emergency Department (ED) patients who are not sick enough to be hospitalized. A previous study found 9% of OU patients have undiagnosed DM and therefore our OU practice is to obtain Hba1c on patients without a history of DM. A typical OU stay is 24 hours, allowing adequate time for screening, education and initiation of treatment if warranted. To conserve resources, we developed a screening tool to allow selective Hba1c testing in the OU.

Methods: We reviewed OU admissions at a tertiary hospital and included patients with no known history of DM and who had Hba1c assessed during their OU stay. Those with Hba1c ≥ 6.5 were categorized as newly diagnosed DM. Previously validated clinical variables were tested in the model; also included were clinical variables readily available in the OU. A model was developed on 2/3 of the cohort and validated on the remaining 1/3.

Results: A total of 2425 patients met inclusion criteria. The final model included BMI, race, family history of DM, age, serum sodium and potassium, glucose on ED arrival and initial systolic blood pressure. Predictive assessment of the model was strong with a C-statistic of 0.823. The model was validated and findings remained strong with a C-statistic of 0.788. Performance at the optimal cut-point yielded a sensitivity of 0.750 and specificity of 0.771.

Conclusions: This screening tool identifies 75% of previously undiagnosed DM patients, while excluding 77% of nondiabetic patients from testing. The model can be used at the bedside or embedded in the electronic medical record to selectively screen for DM. There is potential to identify large numbers of previously undiagnosed DM in the OU and the typical 24-hour stay allows time for education and treatment to be initiated.

Cost-Savings Associated with Digitally Enhanced Insulin Therapy

ISRAEL HOODISH, STANLEY G. BISGAIER, EMILY UNGER, MARY M. AUSTIN, Ann Arbor, MI, Livonia, MI.

Improved glycemic control in patients with type 2 diabetes (T2D) is associated with avoidance of complications and reduced healthcare costs. Yet for decades, most patients have not achieved treatment goals and a third have A1C<9%. The d-Nav® Insulin Guidance Service facilitates scalable attainment and maintenance of therapy goals without increasing provider burden. d-Nav is a handheld device that automatically titrates insulin dosage based on the patient’s glucose readings obtained using the d-Nav device. Additionally, the service includes dedicated support of care specialists and pharmacological optimization if A1c improves. This 9-month study assessed the financial impact of the d-Nav service on diabetes related costs in sub-optimally control patients with T2D. We enrolled 218 insulin-treated patients, 193 of whom completed the 3-month follow-up. Thus far, 156 have completed the study. See Figure for A1c changes and patient satisfaction. Furthermore, 88% have chosen to enroll in a 12-month extension. Direct savings was estimated at $6,172 per patient per year (PPPY) for patients using branded medications and $1,736 PPPY across the entire cohort (p<0.001). Given the simplicity of use for the patient and no added provider burden, expansion of such a service may lead to a sizable reduction in cost.
HEALTH CARE DELIVERY—ECONOMICS/QUALITY IMPROVEMENT

1328-P
Culturally Specific Diabetes Care Reduces Disparities in Metabolic Control
KA HEI KAREN LAU, DAVID M. POBER, SANJEEV N. MEHTA, WILLIAM C. HSU, GEORGE L. KING, Boston, MA

Culturally specific care for Asian Americans (AA) with diabetes may reduce their healthcare disparities and improve outcome. One-year outcomes of an integrated clinic for AA at a tertiary diabetes center previously showed more patients attaining A1C <7% and composite A1C, blood pressure (BP) and cholesterol (ABC) goal than whites in the general Adult Diabetes clinic. In a follow-up study to observe the clinical performance over 4 years, data for patients with T2DM who came during January 1, 2013 to December 31, 2016 were compared among AA in Asian Clinic (AAC, n=162), AA in general Adult Diabetes Clinic (AAD, n=118), and whites in Adult Diabetes Clinic (WAD, n=2846). There was no significant difference in baseline A1C. Patients in AAD were younger (P=0.0003) and diagnosed at an earlier age (P=0.04). Patients in AAC had the lowest BMI of 25.6 kg/m² (P<0.0001). The majority of patients in AAC use English as a second language and had lower income. After one year, 37% of patients in AAC achieved the ABC goal, compared to 31% in AAD (P=0.29) and 28% in WAD (P=0.03). Clinical outcomes in AAC were compromised in 2014-2015 in parallel to a transient reduction in Asian Clinic providers. The percentage of AAC patients achieving the ABC goal dropped to 29% (P=0.008) and 23% (P<0.001) in 2014 and 2015 respectively. With the restoration of adequate staffing in 2016, the percentage of AAC patients reaching the ABC goal in 2016 increased to 26%, which is comparable to AAD and WAD (P>0.85). Percentage of patients with A1C <7% was not significantly different among groups at the end of the study (P>0.25). Despite financial and language difficulties, staff providing clinical care tailored to the need of AA, the AAC was able to reduce healthcare disparity in metabolic outcomes in Asian Americans with diabetes over a long duration.

Supported By: National Institutes of Health (P30DK036836)

1329-P
WITHDRAWN
Cost Savings Associated with Usage and Blood Glucose Control for Members of the Livongo for Diabetes Program

JENNIFER BOLLYKY, WEI LU, JENNIFER SCHNEIDER, CHRISTOPHER WHALEY, Mountain View, CA, Santa Monica, CA

Background: Novel technologies to support real-time self-management of chronic conditions are of interest to entities bearing financial risk for healthcare costs. The Livongo Diabetes Program offers patients with diabetes (1) a cellular-enabled, two-way messaging device that measures blood glucose, (2) free unlimited BG test strips; and (3) access to Certified Diabetes Educators for real-time support and goal setting. Previous work has shown decreased medical costs of $838mpm for Livongo members vs. matched controls during first year of program. This study uses biometric and claims data to investigate the association between use of the Livongo program, BG control and medical spending among a commercially insured population of diabetes patients.

Methods: We compared medical spending and clinical outcomes for Livongo users (n =2027) with matched non-Livongo users (n=8385) for 12 months before and after the launch of the Livongo program using multi-variant instrumental variable regression models that included controls for patient demographics (e.g., age, gender) and risk characteristics (e.g., comorbidity index, prior-period medical spending and program usage).

Results: Following launch of Livongo, risk-adjusted total spending for users and non-users decreased by 15.9%. Launch of Livongo led to a risk-adjusted 76.2% increase in the monthly use rate of Livongo. A 10% increase in the monthly Livongo usage rate is associated with a 2.1% decrease in medical spending associated (p<0.01), which was driven by a 2.9% reduction in spending on office-based services. Mean monthly medical spending for users with mean BG>154mg/dL ($505.86 vs. $681.01, p=0.02).

Conclusion: Patients with diabetes enrolled in the Livongo program for 12 months experience medical cost savings associated with improved BG control. Cost savings for Livongo program users are primarily due to decreased spending on outpatient visits.

Impact of Hyperglycemia on 30-Day Readmission Rates

MARY GAINES, RICHARD E. PRATLEY, Maitland, FL, Orlando, FL

Background: The Centers for Medicare and Medicaid (CMS) Hospital Readmissions Reduction Program (HRRP) aims to reduce 30-day readmission rates for patients with acute myocardial infarction, heart failure, pneumonia, chronic obstructive pulmonary disease and hip/knee arthroplasty. The impact of hyperglycemia on readmission rates for these diagnoses is not known.

Methods: We analyzed 30-day readmission rates for patients discharged from Florida Hospital Orlando with CMS HRRP diagnoses from July 1, 2014 through June 30, 2017. Subjects were grouped according to eligibility (2 point-of-care glucometers within 24 hours) for our glyemic monitoring program (GMP) or not (non-GMP). The GMP group was further divided into controlled (C-GMP, mean glucose during hospitalization 70-180 mg/dL) and hyperglycemic (H-GMP, mean glucose > 180 mg/dL) groups.

Results: The GMP group had significantly higher readmission rates than the non-GMP group, as did the H-GMP group relative to the C-GMP group (Table). These differences remained significant after adjusting for difference in age, sex, diagnosis, case mix index and other factors in logistic regression analyses.

Conclusion: Hyperglycemic patients discharged with a CMS HRRP diagnosis have higher 30-day readmission rates. Strategies to prevent readmission should target glycemic control during and after hospitalization.

Impact of Diabetes Mellitus on Outcomes of Patients Undergoing Autologous Stem Cell Transplantation for Multiple Myeloma in the U.S.

KRISHMITA SIWAKOTI, SMITH GIRL, VIJAY BHATT, New Haven, CT, Omaha, NE

High dose chemotherapy followed by Autologous Stem Cell Transplantation (Auto-SCT) is considered standard of care for most patients with Multiple Myeloma (MM) in the U.S. However, recent evidence suggests that diabetic patients with MM are less likely to receive Auto-SCT due to concerns for higher toxicity. We sought to determine the impact of diabetes on in-hospital outcomes of MM patients undergoing autoSCT. We queried the Nationwide Inpatient Sample (NIS) from the years 2009-2011 to identify all adult hospitalizations with MM and auto-SCT. Diabetic status was ascertained using ICD-9 diagnostic codes. Primary and secondary outcomes were in-hospital mortality and length of stay (LOS) or costs of hospitalization (COH) respectively. Univariate methods included chi-square test and t-test where appropriate. Multivariate analysis was done using Generalized Linear Mixed Model (GLMM) to account for clustering in the dataset. All p-values were two sided and level of significance was chosen at 0.05. A total of 2868 (14,153 estimated) hospitalizations for MM related auto-SCT was identified, out of

Table.

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Utility Improvement</th>
<th>QALY Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved work/school ability</td>
<td>0.059</td>
<td>0.024</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.031</td>
<td>0.013</td>
</tr>
<tr>
<td>Low energy patient</td>
<td>0.022</td>
<td>0.009</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>0.021</td>
<td>0.009</td>
</tr>
<tr>
<td>Paroxysmal tic attack</td>
<td>0.015</td>
<td>0.005</td>
</tr>
<tr>
<td>Pancreas damage</td>
<td>0.009</td>
<td>0.002</td>
</tr>
<tr>
<td>Renal damage</td>
<td>0.073</td>
<td>0.024</td>
</tr>
<tr>
<td>Trust in health care</td>
<td>0.031</td>
<td>0.012</td>
</tr>
<tr>
<td>Improved physical activity</td>
<td>0.041</td>
<td>0.015</td>
</tr>
<tr>
<td>Disruption in body composition</td>
<td>0.007</td>
<td>0.002</td>
</tr>
<tr>
<td>Disruption in body composition</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Improved blood sugar control</td>
<td>0.010</td>
<td>0.003</td>
</tr>
<tr>
<td>Improved mental health</td>
<td>0.006</td>
<td>0.000</td>
</tr>
<tr>
<td>Improved quality of life</td>
<td>0.001</td>
<td>0.000</td>
</tr>
</tbody>
</table>

1331-P

Patient Quality of Life and Benefits of Leptin Replacement Therapy (LRT) in Generalized and Partial Lipodystrophy (GL, PL) treatment: evidence from the Leptin in Lipodystrophy (LIT) study

OMER A. ALL, KEZIAH GOK, KRISTINA S. SHAMPANER, EDWARD TUTTLE, CHARLES GERRITS, REBECCA BROWN, Menlo Park, CA, Boston, MA, Cambridge, MA, Bethesda, MD

Effects of LRT on metabolic disease in GL and PL have been studied; however, little is known about consequences of GL and PL, or the effect of LRT, on quality of life (QoL).

To characterize health utility consequences of GL and PL attributes on patients, a discrete choice experiment (DCE) (following a tutorial on the disease) was conducted with 1,000 members of the general population. Multinomial logit regression was used to estimate utility decrements associated with each attribute using an approach similar to Bansback et al. (2012).

Results were combined with data on prevalence of attributes before and after 1 year of LRT, derived from a retrospective chart review, to assess overall QoL consequences of GL and PL, and the impact of LRT in Quality-Adjusted Life Years (QALYs).

Overall, QALY gains associated with LRT were estimated to be 0.423 across all patients. Impaired work/school ability, hyperphagia and organ damage were the largest contributing attributes.

A subgroup analysis for GL and PL found total QALY gains associated with LRT were 0.423% and 0.413%, respectively. This study indicates that lipodystrophy is associated with a large QoL decrement and that the benefits of LRT may be substantial in these patients. Attribute utility decrements appear to be consistent with those reported in other research (e.g., for diabetes), yet the cumulative impact of attributes makes the burden of GL and PL high.

Table.

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Gain (QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved work/school ability</td>
<td>0.059</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.031</td>
</tr>
<tr>
<td>Low energy patient</td>
<td>0.022</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>0.021</td>
</tr>
<tr>
<td>Paroxysmal tic attack</td>
<td>0.015</td>
</tr>
<tr>
<td>Pancreas damage</td>
<td>0.009</td>
</tr>
<tr>
<td>Renal damage</td>
<td>0.073</td>
</tr>
<tr>
<td>Trust in health care</td>
<td>0.031</td>
</tr>
<tr>
<td>Improved physical activity</td>
<td>0.041</td>
</tr>
<tr>
<td>Disruption in body composition</td>
<td>0.007</td>
</tr>
<tr>
<td>Disruption in body composition</td>
<td>0.000</td>
</tr>
<tr>
<td>Improved blood sugar control</td>
<td>0.010</td>
</tr>
<tr>
<td>Improved mental health</td>
<td>0.006</td>
</tr>
<tr>
<td>Improved quality of life</td>
<td>0.001</td>
</tr>
</tbody>
</table>

1330-P

Impact of Hyperglycemia on 30-Day Readmission Rates

MARY GAINES, RICHARD E. PRATLEY, Maitland, FL, Orlando, FL

Background: The Centers for Medicare and Medicaid (CMS) Hospital Readmissions Reduction Program (HRRP) aims to reduce 30-day readmission rates for patients with acute myocardial infarction, heart failure, pneumonia, chronic obstructive pulmonary disease and hip/knee arthroplasty. The impact of hyperglycemia on readmission rates for these diagnoses is not known.

Methods: We analyzed 30-day readmission rates for patients discharged from Florida Hospital Orlando with CMS HRRP diagnoses from July 1, 2014 through June 30, 2017. Subjects were grouped according to eligibility (2 point-of-care glucometers within 24 hours) for our glyemic monitoring program (GMP) or not (non-GMP). The GMP group was further divided into controlled (C-GMP, mean glucose during hospitalization 70-180 mg/dL) and hyperglycemic (H-GMP, mean glucose > 180 mg/dL) groups.

Results: The GMP group had significantly higher readmission rates than the non-GMP group, as did the H-GMP group relative to the C-GMP group (Table). These differences remained significant after adjusting for difference in age, sex, diagnosis, case mix index and other factors in logistic regression analyses.

Conclusion: Hyperglycemic patients discharged with a CMS HRRP diagnosis have higher 30-day readmission rates. Strategies to prevent readmission should target glycemic control during and after hospitalization.

Table.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-GMP</th>
<th>GMP</th>
<th>C-GMP</th>
<th>H-GMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>17675</td>
<td>17008</td>
<td>11120</td>
<td>5886</td>
</tr>
<tr>
<td>Female %</td>
<td>53.9%</td>
<td>49.8%</td>
<td>49.7%</td>
<td>49.9%</td>
</tr>
<tr>
<td>White %</td>
<td>78.5%</td>
<td>71.8%</td>
<td>71.0%</td>
<td>73.3%</td>
</tr>
<tr>
<td>Age (years)</td>
<td>67</td>
<td>68</td>
<td>69</td>
<td>67</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.2</td>
<td>88</td>
<td>85.5</td>
<td>92.7</td>
</tr>
<tr>
<td>Case Mix Index</td>
<td>1.49</td>
<td>2.07</td>
<td>2.31</td>
<td>1.61</td>
</tr>
<tr>
<td>30-Day Readmission Rate</td>
<td>14.4</td>
<td>21.5**</td>
<td>21.1</td>
<td>22.3*</td>
</tr>
</tbody>
</table>

* P<0.05, ** P<0.01 in risk-adjusted logistic regression analyses.
which 13% had diabetes. The mean age was 58 ± 8.7 years, 43% females and 57% whites. The overall in-patient mortality rate was 1.78% whereas mean LOS and COH was 17 days and $160,720 respectively. Diabetes did not impact inpatient mortality (1.31% vs. 1.85%; p = 0.45), LOS (18 vs. 17.6 days; p = 0.33) or COH ($160,665 vs. $160,728; p = 0.99). Similar results were seen on GLMM for in-hospital mortality (Adjusted Odds Ratio, AOR 0.67, 95% CI 0.26-1.75; p = 0.42) after adjusting for patient age, sex, race, comorbidity, insurance status) and hospital characteristics (bedsize, location, teaching status). Our large U.S. population-based study suggests that diabetic patients with MM undergoing Auto-SCT have similar in-hospital outcomes compared to their nondiabetic counterparts. Future studies should explore the incidence of other treatment related complications in this population.

**PEDIATRICS—OBESITY AND TYPE 2 DIABETES**

**Moderated Poster Discussion:** Metabolic Parameters—Risk Factors for Type 2 Diabetes, Cardiovascular Disease, and Cognitive Development? (Posters: 1334-P to 1339-P), see page 17.

### 1334-P

#### Childhood Metabolic Markers Are Associated with Performance on Cognitive Tasks in Young Children—The Healthy Start Study

ALLISON L.B. SHAPIRO, GRETIA WILKENING, JASON R. TREGELLA, JENNY L. KALBORG, BRANDY RINGHAM, ALEXANDRA V. STAMATOIU, ALEXIS BANNING, DANA DABELEA, Aurora, CO; Denver, CO

A substantial body of literature has implicated metabolic health as a significant contributor to cognitive functioning in adults. However, this has not been investigated among young children whose cognitive functions are still developing. Using data from 4 to 9-year-old healthy children participating in the Healthy Start Study, an ongoing pre-birth cohort, we tested the hypothesis that current metabolic parameters (fasting glucose, insulin and Homeostatic Model of Assessment for Insulin Resistance (HOMA-IR) levels) are inversely associated with performance on cognitive tasks, measured via the NIH Toolbox cognition battery. Fully corrected T-scores for inhibitory control (Flanker task), cognitive flexibility (Dimensional Change Card Sort test), and language (Picture Vocabulary test) were obtained. General linear models were used to test the associations between child metabolic markers and cognitive test scores. All models were stratified by race/ethnicity (n = 53 non-Hispanic white (NHW); n = 45 others) and adjusted for APGAR scores at birth. Among NHW children, fasting glucose, fasting insulin, and HOMA-IR were inversely associated with scores for inhibitory control (β = -3.16, p = 0.003), while fasting glucose was also associated with lower language scores (β = -3.86, p = 0.05). Among children of other racial/ethnic groups, only fasting glucose was significantly associated with lower cognitive flexibility scores (β = -4.19, p = 0.05). Our data suggest that metabolic health may impact cognitive development in young children. Further work is needed to replicate these findings and explore the neural underpinnings of these associations.

**Supported By:** National Institute of Diabetes and Digestive and Kidney Diseases; National Institute of Mental Health

### 1335-P

#### Time to Glucose Peak during Oral Glucose Tolerance Test (OGTT) and Pathophysiological Biomarkers of Type 2 Diabetes in Obese Youth

JOIN YOUNG KIM, HALA TAFIU, FIDA BACHA, SARA MICHALISZYN, SILVA ARSLANLIAN, Pittsburgh, PA; Beirut, Lebanon; Houston, TX; Youngstown, OH

The time to glucose peak occurring at or after 30 min. during an OGTT identifies physiologically distinct groups of adults with differences in insulin sensitivity (IS) and secretion and risk of prediabetes and type 2 diabetes. We stratified 102 obese nondiabetic youth (age 15.0 ± 0.2 years; 49 M/53 F; 42 black/60 white) to Early-peak (EP) vs. Late-peak (LP) according to time to reach peak glucose (at 30 min. vs. >30 min.) during an OGTT and assessed the relationship to clamp-derived biomarkers of youth type 2 diabetes risk. Hepatic β[6] (β[6]glycogen) and peripheral IS (3-hour hyperinsulinemic (80 mU/m2/min)-hyperglycemic clamp), insulin secretion [2-hour hyperglycemic (225 mg/dL) clamp], β-cell function (BCC) relative to IS and body composition were compared. The LP group had lower hepatic and peripheral IS, lack of compensatory increase in 1st and 2nd phase insulin secretion and impaired BCC relative to IS compared with the EP group (Table), with similar fasting glucose and insulin, BMI percentiles and % body fat. In obese nondiabetic youth, the time to glucose peak during an OGTT reflects pathophysiological alterations associated with risk of type 2 diabetes. The risk imparted by a Late-peak glucose, independent of fasting glucose and insulin level, is mirrored in lower in vivo insulin sensitivity and impaired β-cell function, two major pathophysiologic biomarkers of youth type 2 diabetes.

**Moderated Poster Discussion**
Complement and Cardiometabolic Risk in Adolescents
ROBERT P. HOFFMAN, MELANIE M. COFENHOWER, CHACK-YUNG YU, Columbus, OH

Background: Adipocytes produce complement C3 and respond to activation products of the complement cascade. Increased complement levels in adults predict future cardiometabolic disease such as type 2 diabetes and myocardial infarction. Since these diseases have their origins in childhood we studied the relationships of complement components, C3 and C4, to cardiometabolic risk factors in healthy, non-Hispanic white adolescents.

Methods: C3 and C4 levels, endothelial function (reactive hyperemia (RH), venous occlusion plethysmography), arterial stiffness (augmentation index (AI), arterial tonometry), lipids, interleukin-6 (IL-6), c-reactive protein, plasma-mimic activator inhibitor 1 (PAI1) insulin sensitivity and secretion (oral glucose tolerance test) were measured in 59 subjects (29 female, age=15.3±1.7 years, BMI%=22.4±5.9 kg/m2, meansSD). BMI percentile, waist circumference and percent body fat (air displacement) were measured to assess adiposity.

Results: C3 correlated with multiple cardiometabolic risk factors including reactive hyperemia (r=0.41, p=0.002), LDL (r=0.34, p=0.012), triglycerides (r=0.56, p<0.001), PAI1 (r=0.30, p=0.023) insulin sensitivity (r=-0.31, p=0.024). C3 tended to correlated with AIX (r=0.25, p=0.074) and insulin secretion (r=-0.24, p=0.079). C4 levels correlated with RH (r=0.28, p=0.043), AI (r=0.26, p=0.074) and IL-6 (r=0.41, p=0.003). Stepwise regression found that C3 levels predicted LDL independent of measures of adiposity and triglycerides in conjunction with waist circumference while C4 levels in conjunction with BMI% predicted AI, and IL-6 in conjunction with waist circumference. Adiposity measures alone predicted RH, HDL, PAI1 and insulin secretion and sensitivity.

Conclusions: These results indicate that obesity induced increases in C3 are likely to play a significant role in the development of adverse lipids with increased plasma triglyceride and LDL levels while C4 plays a role in the development of increased arterial stiffness and inflammation.

Supported By: American Heart Association; National Institutes of Health

Valine Metabolism Is Altered in Obese Adolescents with Polycystic Ovary Syndrome and Relates to Insulin Sensitivity
ANNIE-MARIE CARREAU, HASSEB RAHAT, YESENIA GARCIA REYES, LAURA PYLE, KRISTEN J. NADEAU, MELANIE CREE-GREEN, Aurora, CO

Polycystic Ovarian Syndrome (PCOS) is common and associated with insulin resistance (IR). The mechanism of IR in PCOS is unclear, likely multifactorial, and may relate to branched-chain amino acids (BCAA) and mitochondrial metabolism. We quantitated differences in BCAA and BCAA breakdown metabolites in plasma samples obtained before and after the euglycemic clamp and a testosterone panel obtained. Nontargeted metabolomics were performed in plasma samples obtained before and after the clamp. T-tests were used for group comparisons, with the Benjamini-Hochberg procedure (false discovery rate (FDR) set to 0.05) to control for multiple testing. Spearman’s correlation coefficient was calculated for BCAA vs. glucose infusion rate (GIR) and free anorexigen index (FAI). The groups had similar demographic, physical activity, diet attributes, HbA1c and lipids. Girls with PCOS had higher FAI and worse IR than controls. FAI related negatively to short chain acylcarnitines C4 (r = -0.74, p=0.0002) and C3 (r = -0.60, p=0.007). During hyperinsulinemia, girls with PCOS had higher valine (FDR-adjusted p=0.04) and lower valine breakdown product D4 butyrylcarnitine (FDR-adjusted p=0.01). End-clamp valine correlated with GIR (r = -0.59, p=0.008) as did C4 butyrylcarnitine (r=0.44, p=0.04). Under hyperinsulinemia, a metabolic signature was revealed in obese girls with PCOS, distinct from that in uncomplicated obesity. Valine was higher in girls with PCOS, while C4 acylcarnitine, its direct mitochondrial metabolite, was lower. Further work is needed to determine if BCAA metabolism is a modifiable target to improve insulin sensitivity or simply a useful biomarker.

Supported By: Diabetes Canada; National Institute of Diabetes and Digestive and Kidney Diseases; Doris Duke Foundation; Boettcher Foundation

Childhood Habitual Sleep Duration Modifies the Polygenic Risk for Obesity through Leptin Pathway — A Longitudinal Study
MING U. JUNJING FU, LANWEN HAN, GE LI, SHAN GAO, STRUAN F. GRANT, BCAMS GROUP, Beijing, China, Philadelphia, PA

Sleep disruption is known to be an obesity risk factor, however, little is known about its interplay with genetic predisposition and pathways involved in obesity pathogenesis, especially in the longitudinal setting. Leveraging a large cohort from the Beijing Child and Adolescent Metabolic Syndrome (BCAMS) study, we aimed to examine a possible sleep-genetic interaction for childhood obesity risk, including longitudinal assessment in a 10-year follow-up and further test if there is any mediation through the leptin pathway. A total of 3,211 children (6-18 years) were recruited from this cohort study. Baseline leptin levels and twelve established adult BMI loci were examined for the associations with habitual sleep duration. After adjusting for pubertal stages, diet score and activity, short sleep duration at baseline was significantly associated with increased overweight/obesity risk at both baseline and follow-up. Genetic predisposition scores, particularly consisting of the central nervous system (CNS) gene variation (GPR5L), were robustly correlated with baseline overweight/obesity in children who slept <8h/day (R=0.01), whereas the association was ablated in those who slept ≥10h/day (P=0.05). Comparable observations were made at follow-up. Mediation analysis revealed a modest direct effect of the GPR5L-sleep interaction on BMI at baseline, while an indirect effect of this interaction was found to be mediated principally through elevated leptin (52.6%); moreover, the mediation effect via leptin remained stable over 10 years. This study provides longitudinal evidence that short sleep duration in children has a long-term impact on the association of polygenic risk for obesity from childhood to young adulthood and leptin pathway explains a key mechanism via a modification effect. Therefore, adequate sleep duration during childhood is important for the early prevention of obesity, especially if there is a genetic predisposition to this transition.

Supported By: Key Program of Beijing Municipal Science and Technology Commission (D1111000000101001, D111100000010103); National Key Research Program of China (2016YFC1004001); Beijing Natural Science Foundation (1721069); Beijing Science and Technology Star Program (20044027, 2011J002); Beijing Chaoyang Hospital (LPY2018166)

ADA-Supported Research  Moderated Poster Discussion

PEDIATRICS—OBESITY AND TYPE 2 DIABETES

T1D and T2D Youth in the Pediatric Diabetes Consortium (PDC) Registers — Comparing Clinical Characteristics and Glycemic Control
WILLIAM V. TAMBOURLANE, FEIYAO CHENG, ROBIN L. GAL, CRAIG KOLLMAN, MICHÈLLE A. VAN NAME, JANE L. LYNCH, BRYCE A. NELSON, New Haven, CT, Tampa, FL, San Antonio, TX, Greenville, SC, PA

Objective: To compare characteristics of youth with T1D (n = 484) vs. T2D (n = 1169) in the PDC.

Methods: Participants were 10 to <21 years at diagnosis. Mann-Whitney U and Chi-square tests were used to compare demographics. Linear regression models were used to compare BMI and HbA1c at diagnosis; logistic regression was used to compare DKA at diagnosis. Post-diagnosis HbA1c differences between cohorts were assessed through repeated measures.

Results: T2D youth were more likely to be female (62 vs. 45%, p<0.001), overweight/obese (99 vs. 16%, p<0.001) and from low income (75 vs. 30%, p<0.001), minority (82 vs. 29%, p<0.001) families. T1D youth were more likely to present with DKA (32 vs. 11%, p<0.001) and have higher mean HbA1c levels (12.0 vs. 10.0%, p<0.001) at diagnosis. More than 70% in both cohorts achieved target HbA1c levels ≤7.5% within 6 months but fewer T1D patients were able to maintain HbA1c target after 6 months (Figure). In 410 participants...
BMI was 33.7 kg/m² and BMI z-score +2.2. 3.3% had ALT ≥ 1.5 upper limit (ULN). At 24 months, changes from baseline in VAT and SAT (by DXA) and AST and ALT were measured at baseline. AST and ALT values were defined as normal (ULN), suggestive of NAFLD, and 0.3% had AST ≥ 1.5 ULN. At 24 months, 185 (45%) required no insulin therapy; c-peptide was 1.45 mmol/l in the subset of 74 measured at baseline.

Objective: In TODAY, metformin + rosiglitazone (M+R) was better in maintaining glycemic control than metformin alone (M) or metformin + lifestyle (M+L), but longitudinal differences in whole body adiposity were small and unrelated to treatment group. As excess visceral adipose tissue (VAT) and nonalcoholic fatty liver disease (NAFLD) are common in T2D, we hypothesized that changes in VAT, subcutaneous adipose tissue (SAT), and liver enzymes, as a marker of NAFLD, would be related to treatment effect.

Methods: TODAY enrolled 689 youth 11-17 y/o with T2D <2 year. In 626 subjects, VAT and SAT (by DXA) and AST and ALT were measured at baseline (BL) and 24 mo. Changes from BL to 24 mo were analyzed in baseline-adjusted repeated measures models.

Results: At BL, mean age was 13.9 y, 66.4% were female, 41.1% Hispanic, 31.1% non-Hispanic black, 20.3% non-Hispanic white (NHW). Mean BMI was 33.7 kg/m² and BMI z-score +2.2. 3.3% had ALT ≥ 1.5 upper limit of normal (ULN), suggestive of NAFLD, and 0.3% had AST ≥ ULN. At 24 mo, BMI, BMI z-score, VAT, and SAT all increased. VAT increased most in M+R and least in M+L (14.2% vs. 3.1%, p<0.001). SAT increased more in M+R (15.7%) than in M+L (6.9%, p=0.0001) or M (8.7%, p<0.001). At 24 mo, between-group differences in VAT:SAT ratio and AST were not significant, but ALT increased more in M+R than M+L (23.1% vs. 2.7%, p=0.015). Sex did not modulate treatment effects on VAT and SAT. Greater increases in VAT occurred in NHW in M+R than M (p<0.001) or M+L (p=0.001). VAT and SAT increases correlated with higher HbA1c (p=0.001), and lower insulin sensitivity (p=0.033), and c-peptide oral disposition index (p=0.038), but did not differ by treatment group.

Conclusion: Unlike in adults, in youth in TODAY, VAT rise was greater in M+R than M+L, VAT and SAT changes were not related to treatment group differences in glycemic control. Increased VAT and SAT correlated with lower insulin sensitivity and secretion. In T2D youth, R may blunt the rise in ALT, but does not lower the VAT:SAT ratio.

Supported By: Novo Nordisk, Boehringer Ingelheim; Takeda Pharmaceutical Company Limited

1341-P
Rosiglitazone Increases Visceral and Subcutaneous Fat in Youth with Type 2 Diabetes (T2D) in the TODAY Study

RUBIN DHALWAL, JOHN A. SHEPHERD, LAUREL EL, DHORMILL, KENNETH C. COPELAND, MITCHELL GEFFNER, JANINE HIGGINS, LYNNNE L. LEVITSKY, KRISTEN J. NADEAU, RUTH S. WEINSTOCK, NEIL H. WHITE, ROCKVILLE, MD, Oklahoma City, OK, Los Angeles, CA, Aurora, CO, Boston, MA, Denver, CO, St. Louis, MO.

Objective: In TODAY, metformin + rosiglitazone (+R) is better in maintaining glycemic control than metformin alone (M) or metformin + lifestyle (M+L), but longitudinal differences in whole body adiposity were small and unrelated to treatment group. As excess visceral adipose tissue (VAT) and nonalcoholic fatty liver disease (NAFLD) are common in T2D, we hypothesized that changes in VAT, subcutaneous adipose tissue (SAT), and liver enzymes, as a marker of NAFLD, would be related to treatment effect.

Methods: TODAY enrolled 689 youth 11-17 y/o with T2D <2 year. In 626 subjects, VAT and SAT (by DXA) and AST and ALT were measured at baseline (BL) and 24 mo. Changes from BL to 24 mo were analyzed in baseline-adjusted repeated measures models.

Results: At BL, mean age was 13.9 y, 66.4% were female, 41.1% Hispanic, 31.1% non-Hispanic black, 20.3% non-Hispanic white (NHW). Mean BMI was 33.7 kg/m² and BMI z-score +2.2. 3.3% had ALT ≥ 1.5 upper limit of normal (ULN), suggestive of NAFLD, and 0.3% had AST ≥ 1.5 ULN. At 24 mo, BMI, BMI z-score, VAT, and SAT all increased. VAT increased most in M+R and least in M+L (14.2% vs. 3.1%, p<0.001). SAT increased more in M+R (15.7%) than in M+L (6.9%, p=0.0001) or M (8.7%, p<0.001). At 24 mo, between-group differences in VAT:SAT ratio and AST were not significant, but ALT increased more in M+R than M+L (23.1% vs. 2.7%, p=0.015). Sex did not modulate treatment effects on VAT and SAT. Greater increases in VAT occurred in NHW in M+R than M (p<0.001) or M+L (p=0.001). VAT and SAT increases correlated with higher HbA1c (p=0.001), and lower insulin sensitivity (p=0.033), and c-peptide oral disposition index (p=0.038), but did not differ by treatment group.

Conclusion: Unlike in adults, in youth in TODAY, VAT rise was greater in M+R than M+L, VAT and SAT changes were not related to treatment group differences in glycemic control. Increased VAT and SAT correlated with lower insulin sensitivity and secretion. In T2D youth, R may blunt the rise in ALT, but does not lower the VAT:SAT ratio.

Supported By: Novo Nordisk, Boehringer Ingelheim; Takeda Pharmaceutical Company Limited
Effect of Liraglutide, Metformin, and Gliclazide on Body Composition in Type 2 Diabetic Patients with Nonalcoholic Fatty Liver Disease—A Randomised Trial

WENHUA FENG, YAN BI, PING LI, TINGTING YIN, CAIXIA GAO, SHANMEI SHEN, LUJUN GAO, CAN JIANG, DALONG ZHU, Nanjing, China; YANAN, China; Shandong, China

Objective: To compare the effects of liraglutide, iraglutide, and metformin on body composition in type 2 diabetes mellitus (T2DM) patients with nonalcoholic fatty liver disease (NAFLD).

Methods: Eighty-five subjects were randomly allocated and received gliclazide (n=27), metformin (n=29), or iraglutide (n=29) monotherapy for 24 weeks. Body composition was measured using dual-energy x-ray absorptiometry.

Results: Liraglutide and metformin reduced weight and total, trunk, limb, android, and gynoid fat mass. However, no significant changes in weight or fat mass occurred with gliclazide. In the liraglutide and metformin arms, weight loss was mainly due to reductions in total, trunk, limb, android, and gynoid fat mass. The stable weight obtained with gliclazide resulted from identical reductions in fat mass and increases in lean tissue mass. Blood glucose concentrations and glycated haemoglobin A1c (HbA1c) levels improved in all treatment arms, but lower HbA1c levels were found with liraglutide and metformin. Serum alanine aminotransferase [ALT] concentrations decreased in all treatment arms, whereas serum aspartate aminotransferase [AST] concentrations reduced with liraglutide and metformin only. For all subjects, weight loss and total, trunk, limb, and android fat mass reductions were positively correlated with reductions in serum ALT and AST concentrations, and reductions in waist circumference were positively correlated with reductions in serum ALT concentrations.

Conclusions: As compared with gliclazide monotherapy, liraglutide and metformin monotherapies resulted in greater weight loss, reductions in body fat mass, and improvements in liver function and blood glucose control among patients with T2DM and NAFLD.

Maternal Gestational Diabetes and Childhood Obesity—A Large Observational Study

JING WANG, LEISHEN WANG, SHUANG ZHANG, HUKUN LUI, JUNHONG LENS, WEIQIN LI, TAO ZHANG, NAN LI, WEI LI, ANDREA RACARELLI, LI-FANG HOU, GANG HU, Tianjin, China; New York, NY; Chicago, IL; Baton Rouge, LA

Previous studies found conflicting results about the associations between the exposure to maternal hyperglycaemia in utero and the later risks of childhood overweight and obesity. The aim of the present study was to compare the children’s body mass index (BMI) growth between offspring exposed to maternal gestational diabetes mellitus (GDM) and those not exposed, and assess the associations between maternal GDM and their offspring’s overweight and obesity risk. We performed a large observational study in 1156 women and their offspring (578 GDM and 578 non-GDM mother-child pairs, matched by their offspring’s gender and age). The mean values of children were 3 years (range 2-9 years old). After adjustment for maternal and children’s characteristics, children born to mothers with GDM during pregnancy had higher mean values of Z scores for BMI-for-age, Z-scores for weight-for-age, waist circumferences, body fat, subscapular skinfold, and suprailiac skinfold, in comparison with their counterparts born to mothers without GDM during pregnancy. Maternal GDM is an independent risk factor of childhood overweight and obesity, and it is associated with children’s faster growth of BMI.

Supported By: European Foundation for the Study of Diabetes; Chinese Diabetes Society; Lilly Programme for Collaborative Research; Tianjin Women’s and Children’s Health Center; Tianjin Public Health Bureau; National Institute of Diabetes and Digestive and Kidney Diseases (R01DK010709 to J.C.); National Institute of General Medical Sciences (US4GM104940 to J.H.)

The Acute Effect of Empagliflozin on Fractional Excretion of Sodium and eGFR in Youth with Type 2 Diabetes

PETTER BJORNSTAD, LORI M. LAFFEL, WILLIAM V. TAMBOBLANE, GUDRUN SIMONS, STEFAN HANTEL, MAXIMILIAN VON EYNATTEN, JYTHIS T. GEORGE, JAN MARQUARD, DAVID CRENEY, Aurora, CO; Boston, MA; New Haven, CT; Biberach, Germany; Ingelheim, Germany; Toronto, ON; Canada

Sodium-glucose cotransporter-2 (SGLT2) inhibition reduces hyperfiltration in adults with T1D, likely by inducing natriuresis, which stimulates tubuloglomerular feedback. This exploratory analysis aimed to examine whether these renal effects occur acutely within 24 hours of SGLT2 inhibition following a single exposure to empagliflozin (EMPA) in youth with T2D. In this single-administration, open-label, randomized, parallel-group study (NCT02121483), 27 patients with T2D (mean age 14.1 years, 67% girls, mean BMI 35.5 kg/m²) received EMPA 5, 10, or 25 mg. The effects of EMPA on fractional sodium excretion (FENa) and estimated GFR (eGFR as assessed by Zappitelli-combined creatinine and cystatin C equation) were investigated by pooling the three doses of EMPA for analyses. At baseline, mean (SD) baseline FENa was 0.55% (0.46), and eGFR was 123.4 ml/min/1.73m² (15.6). After a single dose of EMPA, the adjusted mean change from baseline in FENa was +0.81% (95% CI 0.27, 1.36; p=0.006). The adjusted mean change from baseline in eGFR was -5.8 ml/min/1.73m² (95% CI -8.3, -2.7; p=0.0006). In eGFR subgroups of interest, eGFR decreased by -6.7 (9.7) ml/min/1.73m² in patients with hyperfiltration (n=8, eGFR >115 ml/min/1.73m²; 95% percentile of eGFR for obese youth in NHNES3) and by -5.9 (6.9) ml/min/1.73m² in patients with normofiltration (n=19). SGLT2 inhibition following a single dose of EMPA was associated with acute natriuresis and attenuation of elevated GFR in youth with T2D, suggesting a reduction in intraglomerular pressure. Further mechanistic studies are required to define changes in renal function, and longer-term trials examining renal protective effects in youth with diabetes are needed.

Supported By: Boehringer Ingelheim

Estimating Plasma Glucose with FreeStyle Libre Pro CGM during OGTT in Youth

NEJLA GHANE, MIRANDA BROADNEY, SHAVONNE M. COLLINS, ELISABETH K. DAVIS, SHEILA BRADY, JACK A. YANOVSKI, Bethesda, MD

Objective: To evaluate the accuracy and practicality of the FreeStyle Libre Pro continuous glucose monitor (CGM) during oral glucose tolerance testing (OGTT) in a nondiabetic pediatric sample.

Background: The FreeStyle Libre Pro CGM has been found, in adults, to have acceptable accuracy compared to lab-measured glucose without requiring individual patient calibrations. No studies have assessed lab-measured glucose accuracy for this CGM in children.

Hypothesis: FreeStyle Libre Pro CGM glucose will not differ significantly from lab-measured plasma glucose during OGTT in youth.

Methods: Healthy weight and overweight volunteers (n = 8; 63% male), aged 7-11y wore FreeStyle Libre Pro Flash CGM for 6 days, with a 2-hour OGTT (1.75mg/kg, max 75g) on day 6. Laboratory (Cobas E600, Roche) measured glucose accuracy for this CGM in children.

The FreeStyle Libre Pro CGM will not differ significantly from lab-measured plasma glucose during OGTT in youth.

Results: AUC for CGM and lab glucose were well correlated (r = 0.91, p=0.006) and did not differ in mean value (p=0.84). CGM and lab glucose readings were not significantly different at any timepoint (all p>0.18). There were no significant systematic or magnitude errors as assessed by Bland-Altman analyses at any timepoint. No adverse events occurred with CGM use and all participants considered the device easy to wear.

Conclusions: The FreeStyle Libre Pro CGM device was well tolerated and, even without individual calibration, provided quantitatively similar glucose readings during OGTT for healthy weight and overweight children when compared to lab-measured glucose. If confirmed in larger studies, this CGM may provide adjunctive data during evaluations of glucose excursions that may be useful for pediatric clinical care and research.

Supported By: Thescher Research Fund
Longitudinal Predictors of Insulin Sensitivity and Secretion during Puberty

MEGAN M. KELSEY, LAURA PYLE, ALLISON M. HILKIN, AIMEE JOHNSON, KRISTEN J. NADAEU, PHIL ZETTLER, Aurora, CO; Denver, CO

All youth experience a transient reduction in $S_t$ during puberty, but little is known about the associated physiology. We previously demonstrated cross-sectionally that insulin-like growth factor 1 (IGF-1) and leptin are associated with $S_t$ early in puberty. We now aim to evaluate longitudinal predictors of $S_t$ and acute insulin response to glucose (AIR$_t$) during puberty.

Methods: Forty-five (47% female) normal-weight (mean BMI %ile 44±22%) ethnically mixed youth entered the study in early puberty ( Tanner [F] 2-3). Study visits, including an IV glucose tolerance test (IVGTT), fasting laboratory studies, and DXA, were performed at T2-3, T4, and T5, based on breast development and testicular volume. Physical activity (PA) was assessed by the 3DPAR (3-Day PA Recall). Repeated measures models were used to test if changes over time in potential predictors (IGF-1, leptin, estradiol, total testosterone, dehydroepiandrosterone-sulfate, PA, and urinary gonadotropins) were associated with changes over time in the outcomes, with and without adjustment for sex and % body fat.

Results: $S_t$ (p=0.04) decreased and AIR$_t$ increased (p=0.12) from T2/3- T5. IGF-1 and leptin were the only significant predictors of change in $S_t$ and AIR$_t$ over time. IGF-1 was associated with both $S_t$ (β=−0.016, p=0.0004) and AIR$_t$ (β=1.40, p=0.002), and remained so after adjusting for sex and % fat (p=0.0007 and 0.004, respectively). Leptin was associated with $S_t$ in univariate analysis (p=0.003) and with both $S_t$ (β=0.238, p=0.003) and AIR$_t$ (β=38.4, p=0.043) after adjustment for sex and % fat.

Conclusions: This is the first study to show a longitudinal relationship between leptin and $S_t$ and AIR$_t$ during puberty independent of sex and body fat, and confirms previous reports of associations between IGF-1 and $S_t$ and AIR$_t$. These results suggest that leptin and IGF-1 may be driving factors for changes in $S_t$ and AIR$_t$ during puberty. Knowledge of normal pubertal metabolism may contribute to understanding of diseases of pubertal onset, such as type 2 diabetes.

Supported By: American Diabetes Association (1-11-JF-23 to M.M.K.); National Institutes of Health (K23HD065702-04); Colorado Clinical Translational Sciences Institute (UL1TR0010824); Children’s Hospital Colorado Research Institute; Colorado Institute of Health (DK048520-13)
PEDIATRICS—OBESITY AND TYPE 2 DIABETES

1352-P
Increased Glucagon, but Reduced GIP Secretion, in Adolescents with Obesity and T2DM
Hjalti Kristinsson, Hannes Manell, Monica Vilhelmsson, Jenny Presto, Carolina Gårdal, Hanna Ritzen, Anders H. Forslund, Sr., Peter Bergsten, Uppsala, Sweden

We have previously reported that insulin and glucagon levels at fasting and during OGTT are increased in obese adolescents as glucose intolerance develops. In adults incretin hormone GIP has been coupled with enhanced glucagon secretion. We hypothesized that the observed elevated glucagon levels in obese adolescents are associated with increased levels of GIP. Total GIP in plasma samples from obese (NGT=7, IGT=9, T2DM=4) and lean (N=8) adolescents was measured at fasting and during OGTT with a newly developed ELISA (Mercodia AB, Uppsala, Sweden). Newly secreted GIP and glucagon were defined as GIP and glucagon area under curve AUC during the first 30 min, AUC$_{0-30}$ Ethical approval was obtained from the Uppsala Ethical Review Board. Fasting GIP levels ± SEM were 4.7 ± 2.9, 3.6 ± 2.0, 2.9 ± 1.7 and 2.2 ± 0.9 pmol/L in lean, obese NGT, obese IGT and obese T2DM adolescents, respectively. During OGTT GIP concentrations peaked at 30 min for all groups (Figure). Highest concentrations were observed throughout the OGTT in lean, followed by obese NGT, obese IGT and obese T2DM adolescents. GIP AUC$_{0-30}$ ± SEM was 1181 ± 197, 920 ± 22, 707 ± 146 and 699 ± 211 pmol/L *min in lean, obese NGT, obese IGT and obese T2DM, respectively. For the same groups glucagon AUC$_{0-30}$ ± SEM was -73 ± 21, -39 ± 43, -3 ± 30 and 91 ± 80 pmol/L *min. Hyperglucagonemia in adolescents developing T2DM does not seem to be driven by enhanced GIP secretion.

1353-P
Variation in Phenotypic Features of Two Siblings with PCS1/C Deficiency—Obesity and Hyperproinsulinemia
Elisabeth K. Davis, Miranda Bruadon, Rebecca Persky, Ahmed Torky, Jack A. Yanovski, Bethesda, MD

Background: Inactivating mutations in the PCSK1 gene encoding prohormone convertase 1/3 (PC1/3) are associated with failure to thrive (FTT) and diarrhea during infancy, a tendency toward childhood obesity, and the potential for development of endocrinopathies throughout life, including hyperproinsulinemia. We describe two siblings with the same inactivating compound heterozygous mutations (c.625G>A and c.473G>A) in PCSK1, but with phenotypes of differing severity affecting both body composition and glucose homeostasis. Methods: After sequencing confirmed inactivating PCSK1 mutations, we assessed the siblings for resultant endocrinopathies of PC1/C deficiency. Results: The siblings, a 9y male (M) and an 11y female (F), had severe early onset FTT and diarrhea. Currently, M has extreme obesity (BMI=36.2 kg/m², >99%), diabetes insipidus, central hypothyroidism (FT4 0.7 ng/dL, TSH 4.8 mIU/L with little diurnal variation), and adrenal insufficiency (peak cortisol post-ACTH 10.8 μg/dL). After an overnight fast, glucose was 64 mg/dL and he had dramatic hyperproinsulinemia (5030 pmol/L, normal <8), far exceeding his fasting insulin concentration (380 pmol/L). Glucose tolerance was better than predicted for his degree of obesity (OGTT 2h glucose 79 mg/dL) and proinsulin remained markedly elevated during the OGTT (6610 pmol/L; normal <200).

1354-P
Adolescents at High-Risk for Developing Type 2 Diabetes and/or Polycystic Ovary Syndrome Can Be Identified Using a Simple Questionnaire while in High School
Sidiya Karakas, Sacramento, CA

Introduction: Family history of type 2 diabetes (T2DM), obesity, acanthosis nigricans, skin tags, hirsutism and/or menstrual irregularities are associated with increased risk for developing T2DM, metabolic syndrome and polycystic ovary syndrome (PCOS). Early identification of adolescents at risk can provide opportunities for timely preventive interventions.

Methods: We created a simple questionnaire (UCD-QUEST) which includes 5 sections: 1.) Anthropometrics; 2.) Signs of insulin resistance (pictures of acanthosis nigricans and skin tags); 3.) Family history of DM; 4.) Menstrual history; 5.) Hirsutism (Figure of an adolescent female marking the areas susceptible to hirsutism). The UCD-QUEST was validated for male adolescents only. The UCD-QUEST was administered to 219 students during the 1st year of the school. Results: Self-reported ethnic distribution of the students was: 35% Hispanic, 20% Asian, 17% white and 15% black. Weight distribution was: 39% overweight (26%, BMI: 25-29.9) or obese (13%, BMI≥30). Family history indicated: 22% had one or more 1st degree relative, and 51% had at least one 2nd degree relative with DM. Acanthosis nigricans or skin tags were reported by 14%, hirsutism by 15%, and irregular periods by 38%. One out of 8 female adolescents (13%) fulfilled the clinical criteria for PCOS, but only 2 students had ever heard of PCOS.

Conclusion: Adolescents who are at risk for developing DM, metabolic syndrome or PCOS can be identified by high-school-based screening using a simple questionnaire. Further research is required to determine 1.) whether focusing preventive efforts to these high-risk metabolic risk adolescents can increase the success of the interventions while cutting cost, and 2.) whether identification of high-risk adolescents can provide multi-generational benefits by creating access to their high-risk families and protecting their offspring.

Supported By: National Center for Advancing Translational Sciences (UL1TR000002)

1355-P
Evaluation of a Family-Based Interactive Lifestyle Intervention to Reduce the Risk of Developing Type 2 Diabetes in the Future (PRE-START Intervention)
Emer M. Brady, Laura J. Gray, Susann Weirauch-Büchner, Charlotte Edwardsen, Deirdre Harrington, Rogerio T. Ribeiro, Andorani Vazeou, Alison L. Northern, Elena Alustiza, Melanie Jane Davies, Leicester, United Kingdom, Leipzig, Germany, Lisbon, Portugal, Athens, Greece, San Sebastian, Spain

Aim: Evaluate the PRE-START intervention in five European countries (UK, Portugal, Spain, Germany and Greece). Methods: The 8 family based interactive workshops aimed to elicit positive lifestyle behavior change in 12-14 year olds. The written curriculum was underpinned by specific learning theories and philosophy. Demographic, biobehavioral, anthropometric and lifestyle behavior measures were collected at baseline, 3 and 6 months. Due to design differences across countries, the analysis assesses changes within each country. Results: 318 participants were recruited (50% male, 69% Caucasian ethnicity). Control group were more overweight than the intervention group (10%). Average time spent doing moderate-vigorous physical activity (MVPA) was 45 minutes/day. A trend towards increased MVPA at 6 months in the UK was observed (18 mins/day). The attendance data for change in MVPA at 6 months indicate a dose response. Those attending at least 4 workshops had significantly higher MVPA compared to those who attended less than 4 (OR:1.74, 95% CI:1.53-2.18). A trend towards clinical and statistical significant reduction in both BMI and weight for all countries.

Supported By: European Commission; Swedish Diabetes Association; Uppsala Regional Research Council

**Supported Research**

**Moderated Poster Discussion**
was observed. The UK observed a non-significant reduction in self-reported sitting time on weekdays (1 hour/day). Eating behaviors improved in each country at 6 months; in Greece increased frequency of eating breakfast, a reduction in the number of days snacks eaten in the UK, a trend across all countries for increased fruit and vegetable consumption.

Conclusion: The intervention is accepted by the target population. The data point to positive emerging trends in changes in health behaviors (both eating and activity) in addition to health outcomes namely a reduction in body weight and BMI. A definitive randomized controlled trial is required to test effectiveness and cost effectiveness of the intervention.

Supported By: European Commission

1356-P
The Association between Breakfast Skipping and the Risk of Obesity, Diabetes, Hypertension, or Dyslipidemia—A Meta-analysis from 44 Trials Including 65,233 Cases and 381,051 Controls
XIU M. MA, YONG KU, Luohu, China

Objective: Many epidemiologic studies have explored the relationship between breakfast skipping and risk of chronic diseases. But the conclusions are inconsistent. The purpose of this study was to assess the association between breakfast skipping and risk of obesity, diabetes, hypertension and dyslipidemia.

Research Design and Methods: A literature search was performed in PubMed, Web of science and Embase for relevant articles update to November 2017. Pooled odds risks (ORs) with 95% CI were used as a measure to calculate the differences for dichotomous data (outcome events: obesity, diabetes, hypertension and dyslipidemia).

Results: A total of 44 papers including 65,233 cases and 381,051 controls were included in the present meta-analysis. Skipping breakfast compared to eating breakfast, the risk of obesity increased significantly, the OR was 1.54 (1.39,1.71). In addition, people who skip breakfast had increased risk of hypertension, diabetes and dyslipidemia, the OR of hypertension was 1.07(1.06, 1.07);the OR of diabetes was 1.16 (1.05, 1.29); the OR of elevated triglyceride was 1.22 (0.99,1.49); the OR of elevated cholesterol was 1.15 (1.07,1.22). Subgroup analysis shows that the OR of obesity was 1.56 (1.25,1.93) in Asia and 1.40 (1.15,1.71) in Europe. Besides, the OR of diabetes was 1.13 (0.98,1.29) in Asia and 1.56 (1.04,2.34) in Europe. And the OR of hypertension was 1.07 (1.07,1.08) in Asia and 1.17 (0.71,1.92) in Europe. There was no significant publication bias was found in the studies identified by both Beggs’s test and Egger’s test.

Conclusion: This meta-analysis confirmed that breakfast skipping positively increases the risk of obesity, diabetes, hypertension and dyslipidemia. In particular, it increases the risk of obesity. In Asia, the risk of obesity is more pronounced. However, Europeans who skip breakfast have a greater risk of diabetes and hypertension.

1357-P
Perceptions of Physical Activity in American-Indian Youth at Risk for Diabetes
HEATHER KIMBLEY, JENNIFER CHADWICK, CHARLOTTE L. COLEMAN, MARY A. TULLIER, LISA D. WOLBERT, KENNETH C. COPELAND, KEVIN R. SHORT, Oklahoma City, OK, Talihina, OK, Soper, OK

American Indians (AI) have high prevalence of diabetes, which might be reduced through targeted lifestyle changes. We conducted an exercise program for AI adolescents at risk for diabetes. We tested whether the participants’ perceptions of physical activity were related to their physical characteristics or exercise participation. Overweight (OW) AI youth (n = 75), 11-20 years old, with low physical activity, were instructed to exercise 3d/week for 16 weeks at tribal centers. Another 39 normal weight (NW) peers from the same communities served as a reference group but did not enter the exercise program. Perceived comfort and enjoyment of physical activity was measured on a 15-item, 5-point scale. Clinical tests included body composition, aerobic fitness (VO2peak), and physical activity (daily steps). Mean perception score was higher (more positive outlook) for NW than OW/respectively), but these barriers did not explain variance in exercise completion (64%) and life stressors (85%) than the NW group (51% and 74%, respectively), and these barriers did not explain variance in exercise com-

1358-P
KIAA2022, a Candidate Gene for Syndromic Diabetes
CAROLINE STEKELBURG, JEAN-LOUIS BLUJIN, FRED SANTONI, ELIZABETH A. O’HARE, NORANN A. ZAGHLUL, VALERIE SCHWITZGEBEL, Geneva, Switzerland

Background/Introduction: Using whole exome sequencing we identified a truncating mutation in the KIAA2022 gene in a child with mental retardation and antibody-negative diabetes. The KIAA2022 gene encodes a large protein of 1516 amino acids, which has no significant homology with other known proteins. KIAA2022 has already been associated to X-linked mental retardation. In this study we analyze the potential contribution of KIAA2022 to diabetes.

Methods: Whole exome capture sequencing was performed using the Illumina HiSeq instrument. We performed RT-PCR and immunohistochemistry. We used the INS-1E cell line for in vitro and zebrafish and mice for in vivo knock down studies.

Results: We confirmed mRNA and protein expression of KIAA2022 in murine and human islets by RT-PCR and immunohistochemistry. KIAA2022 partially co-stained with insulin in pancreatic sections. In vitro experiments with INS-1E cells showed that KIAA2022 is highly expressed during cell division and after stress induction by H2O2. To characterize KIAA2022 function in vivo, we performed knock down studies in zebrafish and found a decrease of the beta cell mass by 40% compared to wild type. The beta cell expansion rate, assessed by culturing zebrafish embryos with and without glucose, lead to a 30% decrease of the expansion rate in the knock-down animals in comparison to the control group. We further used the CRISPR Cas9 technology to disrupt the KIAA2022 gene in mice. The knockout mice showed smaller islets and DNA damage signals in islets in comparison to the control mice. The i.p. glucose tolerance tests at twelve weeks of age showed glucose intolerance in mutant in comparison to wild type mice.

Conclusion: In vitro experiments using INS-1E cells suggest that KIAA2022 may play a role in cell division and in DNA damage signaling or repair. The KIAA2022 knock down experiments lead to a decrease of the beta cell mass and glucose-induced expansion rate in zebrafish and DNA damage signals in beta cells of mutant mice as well as glucose intolerance.

Supported By: Swiss National Science Foundation

1359-P
Obstructive Sleep Apnea in Pediatric Type 2 Diabetes—Prevalence, Demographics, and Screening Practices
KRISTAL A. MATLOCK, YUPING GUO, JANE C. KHOURY, NEEPA GURBANI, NANCY A. CRIMMINS, Cincinnati, OH

Background: Managing pediatric type 2 diabetes (T2D) requires provider proficiency in addressing co-morbidities. Adults with T2D are at high risk for obstructive sleep apnea (OSA) but data is limited in children. Study aims were to 1) develop a screening process to assess OSA symptom prevalence in children with T2D and 2) characterize patients with T2D and proven OSA (confirmed by polysomnography [PSG]).

Methods: Michigan Sleep-Disordered Breathing Questionnaire was implemented for patients age 8-18 years with T2D (2017). A score >0.33 defined positive screening for OSA symptoms, resulting in Sleep Medicine referral. Data collected included age, sex, race/ethnicity, duration of T2D, surgical and medication history, body mass index (BMI), blood pressure, lipid profile and hemoglobin A1c. Patients with positive screenings were followed prospectively to describe clinical course.

The same data was collected on patients with T2D and proven OSA via retrospective chart review (2010-2016). Wilcoxon rank sum or Fisher’s exact test were used to compare 1) patients with and without OSA symptoms and 2) patients with and without proven OSA.

Results: Over 10 months, 43 children with T2D completed OSA screening. Forty percent (17/43) screened positive for OSA symptoms leading to referral. Thus far, four children have completed PSG; three had OSA and 1 had

Moderated Poster Discussion ADA-Supported Research
Late Reactive Hypoglycemia (RHG) as a Common Early Sign of Glycometabolic Risk in Adolescents ROBERT P. HOFFMAN, MELANIE M. COPENHAKER, CHACK-YUNG YU, Columbus, OH

Background: Although not usually manifest until adulthood, evidence indicates that cardiometabolic disease has its origins in pediatrics. If we are truly to decrease cardiometabolic disease we must understand the pathophysiology of cardiometabolic risk in childhood. Individuals with the F polymorphism of the complement C3 gene have increased rates of myocardial infarction and athero-sclerosis. Individuals with increased gene copy number of the complement C4 long and A genes have decreased longevity.

Methods: C3 F vs. S genotype and C4A, C4B, C4L and C4G gene copy number were measured in 59 non-Hispanic white subjects (29 female, age: 15.3±1.7 years, BMI: 22±4.1±5.9 kg/m2, mean±SD). Endothelial function (reactive hyperemia [RH], venous occlusion plethysmography), arterial stiffness (augmentation index [AI], arterial tonometry), lipids, interleukin-6 (IL-6), c-reactive protein, plasminogen activator inhibitor 1 (PAI-1) insulin sensitivity and secretion (oral glucose tolerance test) were used to assess cardiometabolic risk. BMI percentile, waist circumference and percent body fat (air displacement) were measured to assess adiposity.

Results: Forty percent of subjects had at least one C3F allele. These subjects were found to have increased waist circumference (78±18 vs. 70±11 cm, p=0.029) and higher HDL levels (55±14 vs. 45±11 mg/dL, p=0.024) compared to those with only the S allele. Increased C4L (r=0.34, p=0.017) and C4A (r=0.33, p=0.019) gene copy number were associated with decreased endothelial function. Multiple linear regression including percent body fat and either C4L or C4A showed that both relationships became more significant.

Conclusions: In adolescent the C3 F polymorphism gene is associated with increased central obesity but surprisingly increased HDL. Increased C4L and C4A gene copy are associated with decreased endothelial function. This could explain their association with decreased longevity.

Supported By: American Heart Association; National Institutes of Health

PEDIATRICS—OBESITY AND TYPE 2 DIABETES

1360-P

Alterations in Novel Signals in the Gut-Adipose Axis—A Pilot Study in Insulin-Resistant Children with Obesity and Biopsy-Proven Nonalcoholic Steatohepatitis MATTHEW D. DI GUGLIELMO, SANA MANSOOR, VIKAS UPPAL, KATRYN N. FURUYA, SEEMA KUMAR, P. BABU BALAGOPAL, Wilmington, DE; Rochester, MN; Jacksonville, FL

Background: Body weight homeostasis and the progression of obesity to comorbidities such as nonalcoholic steatohepatitis (NASH), type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) involve the gut-brain axis, a complex and highly coordinated system of peripheral appetite hormones and centrally mediated neuronal regulation. Data on the role of the gut-adipose axis in children with obesity-related comorbidities are sparse.

We determined novel signals in the gut-adipose axis such as pro-uroguanylin (PUG) produced in the gut and spexin, predominantly produced in white adipose tissue with traditional appetite/satiety hormones in insulin-resistant children with obesity. We measured a range of signals from fat pads and using dietary BPA exposure at doses comparable to human exposure levels.

Methods: A total of 29 children (age: 8-17 years) in three groups, normal weight (NW; n=11; BMI<85th%), obese (n=9; BMI>95 th%) and biopsy-proven NASH (n=9; NAS-score≥2) were studied. Spexin, PUG, leptin, total (T)- and high molecular weight (HMW)-adiponectin and insulin were measured.

Results: Spexin, PUG and both T and HMW adiponectins were lower in children with NASH compared to both children with simple obesity and their NW counterparts, while leptin and insulin were higher (p<0.05). Spexin/leptin ratio and concentration of PUG were significantly lower (p<0.05) in children with NASH vs. simple obesity, whereas leptin and insulin were higher (p<0.05).

Conclusions: Lower concentrations of novel signals such as PUG and spexin in the current study suggest that perturbations in the gut-brain axis occur at an early age in the clinical course of obesity and NASH. The potential role of these novel gut-adipose axis signals, by themselves or in unison with other factors, in diagnosing and/or monitoring the development and/or progression of obesity-related comorbidities such as NASH, T2DM and CVD as well as the potential development of more directed therapies appears to be promising and warrants further studies.

Supported By: American Diabetes Association (1-14-CE-04 to P.B.B.)

1362-P

Paternal Bisphenol A Exposure Alters Offspring Glucose Tolerance in a Time, Dose, and Sex-Specific Manner CETEWAYO S. RASHID, AMITA BANSAL, REBECCA A. SIMMONS, Philadelphia, PA

As it is becoming increasingly accepted that maternal exposure to the ubiquitous environmental pollutant bisphenol A (BPA) predisposes offspring to metabolic impairments, paternal contribution in this context remains unresolved. To investigate a relationship between paternal BPA exposure and offspring obesity and glucose tolerance, a mouse model was developed using dietary BPA exposure at doses comparable to human exposure levels (7% Corn Oil diet [Control], 10 µg/kg/day [Lower BPA], and 10 mg/kg/day [Upper BPA]). Two exposure windows were investigated: 1.) direct exposure of male mice beginning at sexual maturation (5 weeks of age) and continuing for 12 weeks prior to mating, and 2.) in utero exposure, in which dams were exposed beginning 2 weeks prior to mating and ending at weaning. F1 males were sired to unexposed females. At 16 weeks of age, offspring from both exposure windows underwent body composition analysis via NMR or DEXA scan as well as glucose tolerance testing. Paternal BPA exposure during adulthood did not affect body weight, adiposity or glucose tolerance in offspring. In utero-exposed sires produced offspring that also had no changes in body weight or adiposity. However, female offspring from the Lower BPA dose were glucose intolerant. Females with glucose intolerance were selected for islet perfusion, and interestingly, those females from Lower BPA dose exhibited enhanced glucose-stimulated insulin secretion compared to controls indicating insulin resistance. These data demonstrate that while paternal BPA exposure after sexual maturity may be metabolically innocuous, paternal BPA exposure during gestation and lactation pre-
citipates sex-specific impairments in glucose tolerance. Further studies are required to describe precisely the glucose homeostatic impairment and elucidate epigenetic changes in sperm associated with phenotypic transmission.

Supported By: National Institutes of Health (R01ES03284732; HD06056)

1364-P Utility of Fibroscan in Screening Overweight and Obese Children at Risk for Nonalcoholic Fatty Liver Disease
KRISTIN A. DAYTON, FERNANDO BRIL, KENNETH CUS, Gainesville, FL

Study Objective: Nonalcoholic fatty liver disease (NAFLD) is associated with elevated risk for metabolic syndrome, type 2 diabetes, cardiovascular disease and cirrhosis. Available diagnostic tools (plasma aminotransferases and liver ultrasound) have low sensitivity. This study screened a broad population of children from an endocrine clinic with a combination of imaging tools and biomarkers previously used only in children with known liver disease. We hypothesized that Fibroscan (an ultrasound based imaging tool for hepatic fibrosis) would correlate well with MR-elastography (MRE) and be a useful adjunct in combination with known biomarkers of fatty liver disease to screen for advanced cases of NAFLD.

Methods: Overweight patients were recruited from pediatric and endocrinology clinics. They underwent liver 'H magnetic resonance spectroscopy, magnetic resonance elastography, liver Fibroscan, and fasting lab studies. Plasma biomarkers analyzed included hemoglobin A1c, lipid panel, AST and ALT levels, cytochrome P450 18 and homeostatic model of insulin resistance.

Results: Twenty seven patients were recruited and analyzed. NAFLD was present in 30% of patients based on Fibroscan ≥7%, however, only one case was confirmed to have fibrosis on MRE. Two patients with positive Fibroscan were unable to undergo MRE. Metabolic markers including A1c and HOMA-IR were worse in NAFLD vs. no NAFLD patients, but only triglycerides and ALT reached statistical significance.

Conclusions: Fibroscan is useful to eliminate fibrosis, but a positive fibroscan must be further evaluated as many false positives occurred. In combination with triglycerides and ALT, this tool may be useful to stratify those patients most at risk for severe NAFLD and those patients requiring evaluation by pediatric gastroenterologists, biopsy, and more intensive intervention.

Supported By: National Institutes of Health; National Center for Advancing Translational Sciences (UL1TR000427)

1365-P Vitamin D Levels Are Associated with Risk Factors for Type 2 Diabe¬tes and Metabolic Syndrome in Chinese Youths
SHAN QIAO, LAWREN HAN, JUNLING FU, GE LI, MING LI, STEVEN M. WILLI, Beijing, China, Philadelphia, PA

Evidence regarding association between vitamin D deficiency and metabolic syndrome (MS) remains controversial and relatively sparse among youth. We aimed to explore the relationship between serum 25-hydroxyvi¬tamin D (25(OH)D) levels and risk factors for type 2 diabetes and MS in Chi¬nese adolescent and young adults. A total of 559 subjects aged 14-28 years with high risk of MS were recruited from the Beijing Child and Adolescent Metabolic Syndrome Study cohort in 2012. All subjects underwent a 2-h oral glucose tolerance test. The concentrations of 25(OH)D, glucose, insulin and lipids were determined. MS was defined by the 2009 harmonized definition. The prevalence of vitamin D deficiency (<20 ng/ml) was 78.3%. After adjusting for age, gender and visiting season, 25(OH)D levels were negatively correlated with percent body fat, LDL-C, fasting and 2h-glucose levels (all p < 0.05). 25(OH)D levels were significantly lower in subjects with obesity, high TG, type 2 diabetes, or MS, compared to their counterparts, respectively (all p<0.05). After adjustment for potential confounders including body mass index, subjects in the lowest vs. highest tertile of 25(OH)D levels was 2.5 times more likely to have MS (Odds 95% CI: 1.13-5.45, p<0.05). Vitamin D deficiency was very common in this young Chinese population with risk for MS. Given the negative association between vitamin D level and car¬diometabolic risk factors, effective sun exposure and vitamin D supplemen¬tation should be encouraged in youths, particular in those with high MS risk.

Supported By: Key Program of Beijing Municipal Science and Technology Com¬mission (D1111000008110100, D1111000006110202) National Key Research Program of China (2017YFC0909801, 2017YFC0909804) Beijing Natural Science Foundation (7172058, 7172059, 7172069) Beijing Science and Technology Star Program (200404227) Novo Nordisk (2011AD02), Bei¬jing Chaoyang Hospital (LPX201606)

1366-P Co-Occurrence of 2+ Early Complications in Type 1 Diabetes—SEARCH for Diabetes in Youth
KATHERINE A. SAUDER, JEANETTE M. STAFFORD, ELIZABETH J. MAYER-DAVIS, ELIZABETH T. JENSEN, SHARON SAYDAH, AMY K. MOTTL, LAWRENCE M. DOLAN, RICHARD F. HAMMAN, JEAN M. LAWRENCE, CATHERINE PHUOCER, SANTICA M. MARCOVINA, RALPH DAGSTINO, JR., DAN ADBELEA, SEARCH FOR DIABETES IN YOUTH STUDY GROUP, Aurora, CO, Winston-Salem, NC, Chapel Hill, NC, Hyattsville, MD, Cincinnati, OH, Pasadena, CA, Seattle, WA

SEARCH reported a high burden of early complications in type 1 diabetes (T1DM). We examined co-occurrence of complications and related risk fac¬tors among 1327 SEARCH T1DM participants aged 10-30 years. Risk factors were assessed at baseline (mean diabetes duration and age = 0.8 and 10.9 years, respectively) and follow-up (7.8 and 18.0 years, respectively). Retinop¬athy (RE1), diabetic kidney disease (DKD), peripheral neuropathy, cardiovas¬cular and autonomic neuropathy (CAN), and arterial stiffness (AS) were assessed at follow-up. We examined co-occurrence of ≥2 complications overall, by type, and within four demographic/metabolic risk factor clusters identified using cluster analysis. Clusters were characterized by worsening risk profiles (Table). Co-occurrence of ≥2 complications was observed in 5.9% of partici¬pants, more frequently than expected by chance (4.4%, p=0.62). Specifically, RET+DKD (0.83% vs. 0.23%), RET+AS (0.98% vs. 0.34%), and AS+CAN (1.81% vs. 1.04%) all co-occurred more frequently (all p<0.05). Prevalence of ≥2 com¬plications increased across risk clusters from 2.3% to 20.8%.

In conclusion, early T1DM complications co-occur more frequently than expected, at a young age and short diabetes duration. A cluster of risk fac¬tors including minority race/ethnicity, lack of private insurance, and poor metabolic profiles identifies groups to target with interventions to reduce complications.

Table. Selected Characteristics and Prevalence of 2+ Complications at Follow-Up by Risk Factor Clusters

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Diabetes</th>
<th>MS</th>
<th>CAN</th>
<th>CRF</th>
<th>AS</th>
<th>AS+RE</th>
<th>AS+CAN</th>
<th>AS+RE+DKD</th>
<th>AS+RE+CRF</th>
<th>AS+RE+DKD+CRF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster 1</td>
<td>171 (6.3)</td>
<td>55 (16.0)</td>
<td>51 (16.3)</td>
<td>40 (12.3)</td>
<td>26 (8.2)</td>
<td>2 (0.6)</td>
<td>4 (1.3)</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Cluster 2</td>
<td>217 (83.1)</td>
<td>395 (77.6)</td>
<td>257 (73.9)</td>
<td>15 (62.5)</td>
<td>0.002</td>
<td>0.002</td>
<td>0.002</td>
<td>0.002</td>
<td>0.002</td>
<td>0.002</td>
</tr>
<tr>
<td>Cluster 3</td>
<td>211 (80.8)</td>
<td>386 (61.2)</td>
<td>222 (64.2)</td>
<td>9 (27.3)</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Cluster 4</td>
<td>30 (11.5)</td>
<td>60 (19.6)</td>
<td>49 (14.3)</td>
<td>7 (20.7)</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Supported By: National Institutes of Health; National Institute of Diabetes and Digestive and Kidney Diseases; Centers for Disease Control and Prevention

1367-P Diabetes Retinopathy (DR) Relates to Complication Risk in Young Persons with T1D
MICHELLE KATZ, GEORGE L. KING, JENNIFER SUN, LORI M. LAFEL, Boston, MA

Young people who develop DR may represent a high-risk group for early development of other complications. In young persons with youth-onset T1D, we evaluated associations between DR status and markers of other T1D complication risk. Youth (N=127), mean age 21.7 ± 2.5 years (range 10.7-31.9), mean T1D onset 6.3 ± 3 years (range 0.5-17.6) underwent DR assessment (ETORS-protocol 7 field fundus photos); renal, neuropathic, and CVD risk screenings; and risk screening by blood/urine studies. DR was classified as none (No DR, 37%), mild nonproliferative (Mild DR, 46%), and more than mild NPro (Advanced DR, 17%). More severe DR was associated with greater age, T1D duration, A1c, and weight status (Table). DR severity was associated with neuropathy, vascular stiffness by pulse wave (aortic AIX), and inflammatory, oxidative stress, and endothelial activation markers (CRP, homocysteine, e-selectin). Paradoxically, greater DR was associated with less PAI-1. After adjustment for age, T1D duration, weight, and A1c by ANCOVA, DR status was asso¬ciated with differences in cooling threshold (7.6, 8.6, 12.3, p<0.003) and e-selectin (39.8, 40.3, 46.0, p=0.2). Young persons with DR have high risk for neuropathic, renal, and CVD complications. While PAI-1 is lower, markers of inflammation and oxidative stress are higher in this group. Optimal glyce¬

Supported By: Key Program of Beijing Municipal Science and Technology Com¬mission (D1111000008110100, D1111000006110202) National Key Research Program of China (2017YFC0909801, 2017YFC0909804) Beijing Natural Science Foundation (7172058, 7172059, 7172069) Beijing Science and Technology Star Program (200404227) Novo Nordisk (2011AD02), Bei¬jing Chaoyang Hospital (LPX201606)

PEDIATRICS—TYPE 1 DIABETES

Moderated Poster Discussion: Complications of Type 1 Diabetes and Management—New Insights (Posters: 1368-P to 1371-P), see page 19.
mic control must be prioritized to prevent or delay DR progression and other complications in young persons with DR.

**Table.** Unadjusted Associations between Clinical Factors and DR Status.

<table>
<thead>
<tr>
<th>Clinical Factor</th>
<th>No of DR (n=47)</th>
<th>Mild of DR (n=59)</th>
<th>Moderate of DR (n=59)</th>
<th>P value ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>18.9/13.3/6.0</td>
<td>19.5/13.8/6.6</td>
<td>17.9/13.8/9.1</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>T1D Duration</td>
<td>11.7/11.7/11.7</td>
<td>11.7/11.7/11.7</td>
<td>11.7/11.7/11.7</td>
<td>.9999</td>
</tr>
<tr>
<td>A1c (%)</td>
<td>6.3/6.3/6.3</td>
<td>6.3/6.3/6.3</td>
<td>6.3/6.3/6.3</td>
<td>.9999</td>
</tr>
<tr>
<td>BMI z score</td>
<td>0.9/0.9/0.9</td>
<td>0.9/0.9/0.9</td>
<td>0.9/0.9/0.9</td>
<td>.9999</td>
</tr>
<tr>
<td>SBP/DBP/Aortic AIx</td>
<td>110/68/2.0</td>
<td>110/68/2.0</td>
<td>110/68/2.0</td>
<td>.9999</td>
</tr>
</tbody>
</table>

**Impact of Intensive Remote Monitoring on Blood Glucose Measurements in a Cohort of T1D Pediatric Patients**

LARA M. GANBRUD, TIMOTHY J. BARNES, DAVID A. WATSON, Saint Paul, MN, Minneapolis, MN

Intensive and frequent contact with diabetes care providers has been shown to improve glycemic control and reduce risk of complications among TID pediatric patients. However, remote monitoring utilizing newer Bluetooth enabled technology has not been fully evaluated. In a randomized clinical trial, 117 children and adolescents with TID were assigned to either intensive remote therapy (IRT) or conventional care (CC) for 6 months. Both groups continued routine clinic appointments quarterly and uploaded blood glucose BS) and device data weekly. Data for patients assigned to IRT were reviewed weekly, and parents were contacted if there was a regimen adjustment indicated. The primary outcome of the trial was change in HbA1c from baseline, but the focus of this summary is weekly BG measurements reported from BG meters. In total, 107 subjects (53 in the IRT group) uploaded weekly data. In the first 26 weeks, patients uploaded data an average of 24.7 weeks. The outcomes of interest were summaries of BG measurements, namely average and standard deviation of BG levels and whether measurements were in, below, or above the target range (70-140 mg/dl). Multiple observations per subject were analyzed using generalized linear mixed effects models. Patients in the IRT group had average BG levels 19.3 mg/dl lower than the CC group (P=0.0007). The difference between standard deviations of BG levels was not statistically significant. IRT increased the odds of BG measurements in the target range (OR 1.25, P=0.0037), as well as the odds of being below the target range (OR 1.47, P=0.0031), presumably because BG levels were lower. The IRT and CC groups had 24.5% and 20.6% of measurements in the range respectively and 4.7% and 3.2% below the range respectively. These results suggest that IRT can lower BG levels in children and adolescents. Given these promising findings, further research is warranted, as this technology has potential to add convenience and efficiency to TID management and increase time in target.

**Grazing in Young Children with Type 1 Diabetes Is Associated with Higher HbA1c**

ROWEN L. SECKOLD, PETER HOWERLY, BRUCE R. KING, KIRSTIN BELL, CARMEL SMART, Newcastle, Australia, Callaghan, Australia, Sydney, Australia

Glycemic control in the young child with type 1 diabetes (T1D) has traditionally been challenging. Unpredictability in appetite and dietary intake has made the achievement of glycemic targets difficult. This study aimed to assess the nutritional quality and dietary behaviors of young children with T1D that attend a clinic that meets glycemic targets in this age group. Carers of children aged <7 years with type 1 diabetes attending a specialist Pediatric Diabetes Service in Australia completed a 3 day food diary and a survey regarding diabetes management and dietary behaviours.

Twenty one children participated (mean age: 4.7 ±1.3y, 57% male, mean BMI: 13.2 kg/m²). Carers of children aged <7 years with type 1 diabetes attending a specialist Pediatric Diabetes Service in Australia completed a 3 day food diary and a survey regarding diabetes management and dietary behaviours.

Young children with type 1 diabetes can achieve target glycemic control and safely dose insulin before meals. Continuous eating episodes were positively associated with HbA1c. Dietary quality remains a concern in this age group.

**Promoting Health Equity in Type 1 Diabetes through Peer Mentorship—Findings from the All for ONE Randomized Controlled Trial**

ASHBY F. WALKER, MICHAEL J. HALLER, MATHWELL J. GUNKA, HEATHER L. MORRIS, CLAUDIA AÑEZ-ZABALA, BRITTANY S. BRUGSEMAN, DANIELLE GILFRE, HENRY ROHRS III, MARK A. ATKINSON, DESMOND SCHATZ, Gainesville, FL

There are tremendous health disparities in type 1 diabetes (T1D) according to socioeconomic status (SES). Moreover, college students with TID, regardless of SES, face serious health risks as they transition to independent living. The All for ONE (Outreach, Networks, and Education) program was piloted as a novel intervention where college students with TID mentored publicly insured teenagers with TID (n=88), treatment and control. Outcome measures for college students and teens included HbA1c, diabetes knowledge, and the validated College Resiliency and Children’s Hope scales. The intervention included daily text reminders for blood glucose monitoring, weekly text exchanges, social events involved with TID education, clinic visits with mentors/mentees and a weekly training course for the mentors. Paired t-tests were used to compare changes from baseline to study conclusion among the college students, and ANCOVA was used to compare changes between intervention and control teens adjusting for baseline. Adjusting for baseline, the mean change in HbA1c was +0.09 (9% increase) in the intervention group, compared to +0.28 (31% increase) in the control group (p=0.61). College students had a mean -0.22 (27% decrease) in HbA1c (p=0.38). Treatment group teens were significantly more likely to attend clinic visits during the pilot than control group teens (p = 0.02*). Exit surveys with mentors, mentees and parents expounded on the program’s success with 98% reporting they wanted to participate again if given the opportunity. The main value of the program was listed by mentors as increased networks with other

**Novel, Culturally Sensitive Shared Group Appointment Program for Hispanic Pediatric Type 1 Diabetes Patients Is Feasible, Improves Technology Uptake, and Has Promising Results on Better Diabetes Outcomes**

ANDREA GERARD GONZALEZ, ANDREA CAROLINA BRADY, GEORGEANNA J. KLINGENSMITH, LAURA PYLE, JESSICA THURSTON, Aurora, CO

Objective: Hispanic patients with type 1 diabetes (T1D) face cultural and language barriers in care that contribute to a high A1C, infrequent use of diabetes technology and risk of complications. Culturally sensitive programs and shared medical appointments (SMAs) have been recognized as effective models of care. Our aim is to develop a culturally sensitive, cost effective SMA model for pediatric Hispanic T1D patients.

Methods: Hispanic patients, ages 1-20, with T1D (n= 88), and their families were recruited to participate in the SMAs. They received routine care appointments alternating with SMAs that included group diabetes education. Teens, ages 12 to 18 attended a separate educational session from parents. Younger children and parents were seen together. A1C, behavioral tools, and use of diabetes technology were measured at baseline and every 3 months for two years. Satisfaction questionnaires were obtained.

Results: 62% of young children and 48% of teens completed the first 2 years of the SMA model of care. Results showed that there was a significant association between age and change in A1C for SMA participants from baseline to year 1 (p = .001) and baseline to year 2 (p < .0001). Participants ≥ 12 years old, had a significant improvement in A1C from baseline to year 1 (p = 0.014) and from year 1 to year 2 (p = 0.007). Participants ≥ 12 years old, also had a change in A1C from year 1 to year 2 (p = 0.008). Technology use increased significantly from baseline to year 2 for participants who were less than 12 years of age (17% to 40% p = .014) and marginally significant for participants who were >11 years of age (10% to 18% p = .083). Participants had a 90% satisfaction rate.

Conclusions: The culturally sensitive SMA proved to be an appreciated, feasible and effective alternative to care for Hispanics with TID. It may prove to be cost-effective and more effective over the long-term if begun shortly after diagnosis.

Supported By: The Leona M. and Harry B. Helmsley Charitable Trust

**1368-P**

**1369-P**

**1370-P**
college students with T1D, by mentees as being able to talk to their mentor about the disease, and by parents as giving their child a confident who understood T1D. This pioneering program concurrently targets two vulnerable populations, establishing critical feasibility for a model that uses routine events of texting, clinic visits, and college curriculum.

Supported By: J&J Center for Health Research

1372-P

Motivational Stage at CGM Initiation is Less Important than Timing of CGM Initiation in Predicting CGM Adherence

KATE VERBEETEN, JASON CHAN, NADIA SOURIAL, MARGARET L. LAWSON, CMM TIME TRIAL STUDY GROUP, JDRF CANADIAN CLINICAL TRIALS NETWORK, Ottawa, ON, Canada, Montreal, QC, Canada

Background: Readiness for making behavioral changes is a key factor determining success in the adoption of technologies like CGM in type 1 diabetes (T1D). SOCRATES (Stages of Change Readiness and Treatment Eagerness Scale-Diabetes Version) can classify individuals into 1 of 5 motivational stages: Precontemplation, Contemplation, Determination, Action and Maintenance. It was used in the CGM TIME Trial, a multicenter pediatric RCT comparing simultaneous pump and CGM (‘SIM’ group) to initiation of CGM 6 months later (‘DEL’ group) (MiniMed Vac™ System).

Aim: To examine the association of SOCRATES scores with 1) AIC at trial entry and 2) CGM adherence and change in AIC 6 months after CGM initiation.

Methods: 97/99 eligible children aged 10-18 years and 136/141 eligible parents completed SOCRATES at trial entry and 6 months. Multivariable linear regression tested the association between motivational stage and 1) child’s AIC at trial entry, and 2) change in AIC and CGM adherence 6 months after CGM initiation, adjusted for randomization group, gender, age, and diabetes duration.

Results: At trial entry, mean adjusted AIC was 1.02% lower for children in Precontemplation than those in Action (p<0.001). The AIC of children whose parents were in Precontemplation was 0.83% lower than those in Maintenance (p=0.02) and 0.35% lower than those in Action (p=0.048). Motivational stage of children and parents at CGM initiation was not associated with CGM adherence or change in AIC 6 months later whereas there was an intervention effect with the SIM group using CGM an additional 3.4 hours per day (p=0.03) compared to the DEL group.

Conclusions: SOCRATES scores were associated with AIC at trial entry, but did not predict future CGM adherence or change in AIC. SOCRATES was a poor measure of readiness for change in children with T1D and their parents who were participating in a clinical trial. CGM adherence was related more to timing of CGM initiation than motivational stage.

Supported By: JDRF Canadian Clinical Trials Network

1373-P

Impact of Target HbA1c Change in Pediatric Participants in the T1D Exchange Clinic Registry

JAMIE WOOD, CLAIRE BOYLE, MARVANNE QUINN, JENISE C. WONG, MICHAEL J. HALLER, BRYCE A. NELSON, MICHAEL J. HALLER, DESMOND SCHATZ, WILLIAM V. TAMBORLANE, LARRY FOX, PRIYA PRAHALAD, SARAH CORATHERS, DAVID M. MAAMS, GUY T. ALONSO, DANIEL J. DESALVO, R. PAUL WADWA, LINDA DIMEGLIO, CINCINNATI, OH, Los Angeles, CA, Gainesville, FL, Greenville, SC, New Haven, CT, Jacksonville, FL, Stanford, CA, Cincinnati, OH, Denver, CO, Houston, TX, Aurora, CO, Indianapolis, IN

In 2014, the American Diabetes Association lowered its recommended HbA1c target for children with type 1 diabetes (T1D) from <8.5% for <6 years, <8.0% for 6-<13 years, and <7.5 for 13<18 years to <7.5% for all ages. To determine if HbA1c change in response, we compared two cross-sectional cohorts of T1D participants in the United States aged <16 years with T1D duration ≥1 year from the T1D Exchange Clinic Registry. The first cohort (PRE) were participants who enrolled between 2010 and 2012 (n=11,788). The second cohort (POST) were participants with an update between 2016 and 2017 (n=9,234). For each age group, mean HbA1c was compared between the cohort using a linear regression model adjusted for age, T1D duration, and socioeconomic status (SES). A comparison of the cohorts can be found in Table 1. Demographic and SES characteristics were similar between the cohorts. More participants in the POST cohort were using insulin pumps and CGMs. Mean HbA1c was similar between the two cohorts for those <6 years, though more participants in the POST cohort met the current HbA1c target. For the 6–<13 and 13–<18 age groups, those in the POST cohort had higher mean HbA1c, with fewer meeting the current HbA1c target (p<0.01).

Thus, despite the lowering of HbA1c targets, glycemic control remains suboptimal in this population.

Supported By: The Leona M. and Harry B. Helmsley Charitable Trust

1374-P

Early and Later C-Peptide Responses during Oral Glucose Tolerance Testing (OGTT) Are Independently and Oppositely Predictive of Type 1 Diabetes (T1D) in Autoantibody-Positive (Ab+) Individuals

HEBA M. ISMAIL, DOROTHY J. BECKER, SUSAN Geyer, PING XU, INGRID LIBMAN, KEVAN C. HEROLD, MARK A. ATKINSON, MARIA J. REDONDO, JERRY P. PALMER, JAY SOSENKO, Pittsburgh, PA, Tampa, FL, New Haven, CT, Gainesville, FL, Houston, TX, Seattle, WA, Miami, FL

A longitudinal study showed that early C-peptide (C-P) responsiveness during OGTTs declined during progression to T1D, whereas later C-P responsiveness increased until the diagnosis was imminent. We examine: 1) whether the baseline C-P response pattern predicts T1D as suggested by the findings from that longitudinal study, and 2) the basis for the higher later C-P response during progression. Baseline 2-hour OGTTs from 670 Diabetes Prevention Trial-type 1 participants (age: 13.8±9.6 years; BMI: 23.3; p<0.001) were at least as predictive as the AUC-C-peptide (inverse association; X2=20.4; p<0.001), a standard prediction measure. In a model including both early and late C-P responses, both remained oppositely predictive of T1D with a stronger overall association (X2=41; p<0.001 for both).

To explain the positive association of greater T1D risk with a high later C-P, we examined the association between the sum of glucose levels from 60-120 min and the 120-60 min C-P; there was a strong positive association (p=0.44; p<0.001). All associations persisted after age and BMI adjustments.

In conclusion, the findings show that later lower and higher late C-P responses are both indicators of risk for progression to T1D. Moreover, the findings suggest that the increasing later C-P response reflects an attempt by the β-cell to compensate for higher glucose levels due to a deficient early C-P response. These findings are similar to the evolution of C-P responses during type 2 diabetes development. Partitioning C-peptide into early and later responses appears beneficial for T1D prediction and for studying β-cell deterioration during progression.

Supported By: National Institutes of Health

1375-P

Associations of Executive Function (EF) with Diabetes Management and Glycemic Control in Teens with Type 1 Diabetes (T1D)

MEREI HANSSENN, ZUJING GUO, LISA VOLKENING, LORI M. LAFFEL, Boston, MA

Background: Management of T1D requires processes of EF such as planning, problem-solving, and task-completion. This study examined associations of EF with T1D management and outcomes in teens with T1D.

Methods: Teens and their parents completed self-report and parent proxy-report versions, respectively, of the Behavior Rating Inventory of Executive Function (BRIEF). Scores >80, as total (Global Executive Composite [GEC]) score or on 2 indices (Behavioral Regulation [BRI] and Metacognition [MI]) indicate EF problems. Parents completed validated scales assessing teen adherence, teen T1D self-efficacy, parent involvement in T1D care, and diabetes-specific family conflict.

Results: The sample (N=169, 54% male) was 15.9±1.3 (±SD) years old and had T1D for 8.4±3.7 years. 67% were pump treated, A1c was 8.5±1.2. Parent reported vs. teen reported GEC scores uncovered 25% vs. 9% of
teens with EF problems (p < 0.01). Teens with EF problems (GEC, BRI, MI) by parent report were less likely to use pump therapy and had higher AIC, poorer adherence, lower T1D self-efficacy, more parent involvement, and greater family conflict (Table).

Conclusions: Parents appear to be more likely than teens to identify teen EF problems. Screening for executive dysfunction in teens with T1D should be considered in order to identify teens in need of family and healthcare team support.

Table.

Glycemic outcomes

<table>
<thead>
<tr>
<th>Glycemic outcomes</th>
<th>HCL Overall</th>
<th>OL Overall</th>
<th>HCL Night</th>
<th>OL Night</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean glucose (mg/dL)</td>
<td>156.3 ± 22.1</td>
<td>177.5 ± 28.5</td>
<td>154.8 ± 29.0</td>
<td>177.6 ± 35.2</td>
</tr>
<tr>
<td>Percent time &lt;54 mg/dL</td>
<td>0.3 ± 0.4</td>
<td>0.6 ± 0.6</td>
<td>0.1 ± 0.4</td>
<td>0.8 ± 1.1</td>
</tr>
<tr>
<td>Percent time &lt;70 mg/dL</td>
<td>2.2 ± 1.9</td>
<td>2.9 ± 2.4</td>
<td>1.0 ± 1.9</td>
<td>2.6 ± 2.5</td>
</tr>
<tr>
<td>Percent time 70-140 mg/dL</td>
<td>47.1 ± 12.3</td>
<td>34.5 ± 13.4</td>
<td>52.5 ± 18.4</td>
<td>32.7 ± 16.7</td>
</tr>
<tr>
<td>Percent time 70-180 mg/dL</td>
<td>52.9 ± 12.9</td>
<td>54.9 ± 12.9</td>
<td>73.8 ± 19.3</td>
<td>53.4 ± 18.8</td>
</tr>
<tr>
<td>Percent time &gt;180 mg/dL</td>
<td>28.7 ± 14.1</td>
<td>42.2 ± 14.7</td>
<td>25.2 ± 19.7</td>
<td>44.0 ± 20.8</td>
</tr>
<tr>
<td>Total night (%)</td>
<td>8.6 ± 8.8</td>
<td>7.1 ± 11.4</td>
<td>8.6 ± 11.7</td>
<td>15.6 ± 15.0</td>
</tr>
</tbody>
</table>

Supported by: Insulet Corporation

1376-P Safety and Performance of the Omnipod® Hybrid Closed-Loop System in Adolescents with Type 1 Diabetes over Five Days Under Free-Living Conditions

GREGORY P. FORLENZA, BRUCE BUCKINGHAM, JENNIFER SHERR, THOMAS A. FEYER, JOON BOK LEE, JASON B. OCONNOR, BONNIE DUMAIS, LAUREN M. HUYETT, JENNIFER E. LAYNE, TRAN S. T., Aurora, CO, Palo Alto, CA, Billerica, MA

The safety and performance of the Omnipod® hybrid closed-loop (HCL) personalized model predictive control algorithm was assessed in adolescents with type 1 diabetes (T1D) using an investigational device over 5 days in a supervised hotel setting under free-living conditions. Eligible participants were aged 6-11.9 y with A1C <10.0% using CSII or MDI. A 7-day open-loop (OL) phase of standard therapy (CSII/MDI) plus CGM use at home preceded the 96 h HCL phase. Meals during HCL were unrestricted, with boluses administered per usual routine. Moderate-intensity exercise was performed for ≥30 min/d. An adaptive approach was used to update participant parameters after the first 48 h of HCL. Fifteen participants (MDI n=3) were (mean ± SD): age 9.9 ± 1.0 y, diabetes duration 5.2 ± 2.0 y, AIC 8.0 ± 0.9% and TDD 1.01 ± 0.24 U/kg. Glycemic outcomes are reported in the Table. The percentage of time 70-180 mg/dL was 14.3% higher during HCL compared to OL overall (HCL 69.2 ± 13.5 vs. OL 54.9 ± 12.8) and 20.4% higher overnight (HCL 73.8 ± 19.3 vs. OL 53.4 ± 18.8). A concomitant reduction in the percentage of time <70 mg/dL occurred during HCL vs. OL overall (HCL 2.2 ± 1.9 vs. OL 2.9 ± 2.4) and overnight (HCL 1.0 ± 1.9 vs. OL 2.6 ± 2.5). The Omnipod HCL system was safe and performed well over 5 days of use in children with T1D under free-living conditions with unrestricted meals and moderate-intensity exercise.

Table.

Glycemic outcomes during Hybrid Closed-Loop (HCL) and Open-Loop (OL) Phases.

<table>
<thead>
<tr>
<th>Glycemic outcomes</th>
<th>HCL Overall</th>
<th>OL Overall</th>
<th>HCL Night</th>
<th>OL Night</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean glucose (mg/dL)</td>
<td>143.8 ± 19.5</td>
<td>162.5 ± 25.9</td>
<td>141.4 ± 28.5</td>
<td>152.9 ± 31.2</td>
</tr>
<tr>
<td>Percent time &lt;54 mg/dL (%)</td>
<td>0.4 ± 0.4</td>
<td>0.8 ± 0.8</td>
<td>0.1 ± 0.2</td>
<td>0.7 ± 1.0</td>
</tr>
<tr>
<td>Percent time &lt;70 mg/dL (%)</td>
<td>2.5 ± 2.0</td>
<td>4.4 ± 4.0</td>
<td>1.3 ± 1.6</td>
<td>6.5 ± 6.6</td>
</tr>
<tr>
<td>Percent time 70-140 mg/dL (%)</td>
<td>54.3 ± 15.8</td>
<td>39.9 ± 14.9</td>
<td>59.5 ± 23.9</td>
<td>41.3 ± 20.1</td>
</tr>
<tr>
<td>Percent time 70-180 mg/dL (%)</td>
<td>79.0 ± 23.0</td>
<td>66.8 ± 15.6</td>
<td>85.4 ± 19.7</td>
<td>62.1 ± 15.7</td>
</tr>
<tr>
<td>Percent time &gt;180 mg/dL (%)</td>
<td>16.5 ± 13.5</td>
<td>35.0 ± 16.2</td>
<td>13.3 ± 18.7</td>
<td>31.4 ± 20.5</td>
</tr>
<tr>
<td>Total night (%)</td>
<td>3.5 ± 5.0</td>
<td>12.0 ± 6.3</td>
<td>3.3 ± 10.0</td>
<td>7.5 ± 7.2</td>
</tr>
</tbody>
</table>

Supported by: Insulet Corporation

1378-P Family History of Diabetes Is Associated with Increased Risk of Recurrent DKA in Pediatric Patients in Rhode Island

JANAKI D. VAKHARIA, SUNGEETA AGRAWAL, JANINE BACIC, LISA S. TOPOR, Providence, RI, Boston, MA

Factors related to recurrent DKA in pediatric patients with DM have been studied previously, with family history (FHx) of DM suggested as a protective factor. We sought to determine associations with DKA recurrence in our pediatric population as the first step in developing an intervention to reduce the frequency of DKA recurrence. In a retrospective chart review, we identified 270 patients admitted for DKA at our institution during a 5 year period. We excluded patients with new onset DM or missing data, identifying 295 DKA admissions amongst 131 patients. Patients were divided into a Recurrence group (n=2 admissions, n=39%) and Non-Recurrence group (1 admission). FHx was significantly associated with Recurrence in both univariate (OR 6.96, p-value <0.0001) and multivariate (OR 8.32, p-value < 0.001) logistic regression analyses. Older age was also significantly associated with Recurrence in both analyses. Younger age at diagnosis and public insurance was only significant in the multivariate and univariate analysis, respectively (Table 1). Family history of diabetes is associated with increased risk of DKA recurrence in our pediatric patients. Larger, multicenter studies are needed to study the relationship between FHx of DM and frequency of DKA admissions. At our center, this data may be used to identify patients at risk, and develop an intervention targeting all household members with DM.
Insulin Treatment and Clinical Outcomes in 67 Participants with Infancy-Onset Diabetes

LISA R. LETOURNEAU, DAVID CARMODY, ANNA M. DENSON, MAY SANYOURA, ROCHIELLE N. NAYLOR, LOUIS H. PHILIPSON, SIRI ATMA W. GREELEY, Chicago, IL, Singapore, Singapore

Infancy-onset diabetes occurs within the first year of life and can be monogenic or autoimmune. We investigated insulin regimens and clinical outcomes through the U.S. Monogenic Diabetes Registry. Relevant data was extracted from medical records collected from the time of diagnosis through the first two years of life. Medical records from 67 individuals were obtained. Clinical characteristics are shown in Table 1. Insulin regimens are reported in Table 2. Most participants stayed on an insulin regimen with the same intensity, ranging from staying on a pump (CSII) to staying on 2 shots of insulin per day. While 30% increased in intensity, 14% decreased (Table 2). Many different regimens appeared to be effective in infants, but further research on greater numbers of patients may show additional advantages to more intense regimens such as CSII.

**Table 1. Clinical Characteristics**

<table>
<thead>
<tr>
<th>Total participants (n)</th>
<th>Current age (years)</th>
<th>Records available</th>
<th>Diagnosis and clinic notes*</th>
<th>Clinic notes only</th>
<th>Diagnosis only</th>
<th>Gender (male)</th>
<th>Ethnicity (self-reported)</th>
<th>Race (self-reported)</th>
<th>Deceased? (yes)</th>
<th>Diabetes etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>67</td>
<td>0.6 (5.1-12.8)</td>
<td>52</td>
<td>12</td>
<td>3</td>
<td>Not Hispanic/Latino 52 (78%)</td>
<td>Hispanic/Latino 8 (12%)</td>
<td>Unknown/not reported 7 (10%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>49 (73%)</td>
<td></td>
<td>Black/African American 2 (9%)</td>
<td>Asian 3 (4%)</td>
<td>Multiple races 6 (9%)</td>
<td>Unknown/not reported 7 (10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>21 (36%)</td>
<td></td>
<td>Triglycerides but unresponsive 7 (33% of above)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8 (12%)</td>
<td></td>
<td>DKA after diagnosis? (yes) 1 (2%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Clinic notes refer to any record after diagnosis up to 2 years of age.

**Table 2. Change in Insulin Regimens from Diagnosis to 2 Years of Life**

<table>
<thead>
<tr>
<th>Diabetes type</th>
<th>Diagnosis of diabetes</th>
<th>Visit closest to age 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPHiusin pump</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin bolus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin pump</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin bolus</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1380-P

Impact of Family-Centered Tailoring of Pediatric T1D Self-Management Resources

ROSANNA V. PAUL-SCHARE, VICTORIA P. RAJAMANNIKA, BETTY A. CHEWNING, MARI PALTA, TOSHA B. WETTENNECK, TIM WYSOCKI, ELIZABETH D. COX, Milwaukee, WI, Madison, WI, Jacksonvill, FL

Background: Experts recommend family-centered self-management approaches that address specific T1D self-management barriers for each child and family. However, no system-level method currently exists to identify and address these barriers.

Objectives: To assess the impact on glycemic control and QoL for the child and parent of a family-centered approach to the delivery of diabetes self-management resources.

Methods: Children 8-16 years old with T1D and their parent(s) were randomized to receive either tailored self-management resources (intervention) or usual care. Our intervention 1.) identified families' self-management barriers with a validated survey, 2.) tailored self-management resources to identified barriers, and 3.) delivered these resources as group sessions coordinated with diabetes visits to optimize convenience, efficiency, and sustainability. Mixed effects models with repeated measures were used to examine the intervention’s impact on A1c and parent and child QoL during the 9-month intervention period and for a year thereafter.

Results: Among 363 potentially eligible families, 267 (74%) consented to participate. Randomization allocated 108 families to usual care and 106 to the intervention. Participants were children (8-12 years, 44%) and teens (13-16 years, 56%). Mean diabetes duration was 5.4 years (sd 3.3) and 14% had an A1c <7.5%. Most families (69%) attended at least 3 of the 4 intervention sessions. No overall intervention effect on A1c or QoL for the child or parent was shown. However, at one site, mean A1c in the year post-intervention declined by 0.059% more per month for intervention group teens than for those receiving usual care (p=0.02). At this same site, mean parent QoL increased by 0.61 points per month more during the intervention for parents of intervention group children than parents of those receiving usual care (p=0.03).

Conclusions: Findings can inform healthcare organizations’ decisions about ways to best deliver diabetes self-management resources.

Supported By: American Diabetes Association (11-17-CT-41 to L.R.L), (1-17-JDF-008 to S.A.W.G.); Novo Nordisk; National Institute of Diabetes and Digestive and Kidney Diseases (R01DK104942, P30DK020595, K23DK094866); National Center for Advancing Translational Sciences (UL1TR000427); Kovler Family Foundation

1379-P

Insulin Treatment and Clinical Outcomes in 67 Participants with Infancy-Onset Diabetes

LISA R. LETOURNEAU, DAVID CARMODY, ANNA M. DENSON, MAY SANYOURA, ROCHIELLE N. NAYLOR, LOUIS H. PHILIPSON, SIRI ATMA W. GREELEY, Chicago, IL, Singapore, Singapore

Infancy-onset diabetes occurs within the first year of life and can be monogenic or autoimmune. We investigated insulin regimens and clinical outcomes through the U.S. Monogenic Diabetes Registry. Relevant data was extracted from medical records collected from the time of diagnosis through the first two years of life. Medical records from 67 individuals were obtained. Clinical characteristics are shown in Table 1. Insulin regimens are reported in Table 2. Most participants stayed on an insulin regimen with the same intensity, ranging from staying on a pump (CSII) to staying on 2 shots of insulin per day. While 30% increased in intensity, 14% decreased (Table 2). Many different regimens appeared to be effective in infants, but further research on greater numbers of patients may show additional advantages to more intense regimens such as CSII.

**Table 1. Clinical Characteristics**

<table>
<thead>
<tr>
<th>Total participants (n)</th>
<th>Current age (years)</th>
<th>Records available</th>
<th>Diagnosis and clinic notes*</th>
<th>Clinic notes only</th>
<th>Diagnosis only</th>
<th>Gender (male)</th>
<th>Ethnicity (self-reported)</th>
<th>Race (self-reported)</th>
<th>Deceased? (yes)</th>
<th>Diabetes etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>67</td>
<td>0.6 (5.1-12.8)</td>
<td>52</td>
<td>12</td>
<td>3</td>
<td>Not Hispanic/Latino 52 (78%)</td>
<td>Hispanic/Latino 8 (12%)</td>
<td>Unknown/not reported 7 (10%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>49 (73%)</td>
<td></td>
<td>Black/African American 2 (9%)</td>
<td>Asian 3 (4%)</td>
<td>Multiple races 6 (9%)</td>
<td>Unknown/not reported 7 (10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>21 (36%)</td>
<td></td>
<td>Triglycerides but unresponsive 7 (33% of above)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8 (12%)</td>
<td></td>
<td>DKA after diagnosis? (yes) 1 (2%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Clinic notes refer to any record after diagnosis up to 2 years of age.

**Table 2. Change in Insulin Regimens from Diagnosis to 2 Years of Life**

<table>
<thead>
<tr>
<th>Diabetes type</th>
<th>Diagnosis of diabetes</th>
<th>Visit closest to age 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPHiusin pump</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin bolus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin pump</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin bolus</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1380-P

Impact of Family-Centered Tailoring of Pediatric T1D Self-Management Resources

ROSANNA V. PAUL-SCHARE, VICTORIA P. RAJAMANNIKA, BETTY A. CHEWNING, MARI PALTA, TOSHA B. WETTENNECK, TIM WYSOCKI, ELIZABETH D. COX, Milwaukee, WI, Madison, WI, Jacksonvill, FL

Background: Experts recommend family-centered self-management approaches that address specific T1D self-management barriers for each child and family. However, no system-level method currently exists to identify and address these barriers.

Objectives: To assess the impact on glycemic control and QoL for the child and parent of a family-centered approach to the delivery of diabetes self-management resources.

Methods: Children 8-16 years old with T1D and their parent(s) were randomized to receive either tailored self-management resources (intervention) or usual care. Our intervention 1.) identified families’ self-management barriers with a validated survey, 2.) tailored self-management resources to identified barriers, and 3.) delivered these resources as group sessions coordinated with diabetes visits to optimize convenience, efficiency, and sustainability. Mixed effects models with repeated measures were used to examine the intervention’s impact on A1c and parent and child QoL during the 9-month intervention period and for a year thereafter.

Results: Among 363 potentially eligible families, 267 (74%) consented to participate. Randomization allocated 108 families to usual care and 106 to the intervention. Participants were children (8-12 years, 44%) and teens (13-16 years, 56%). Mean diabetes duration was 5.4 years (sd 3.3) and 14% had an A1c <7.5%. Most families (69%) attended at least 3 of the 4 intervention sessions. No overall intervention effect on A1c or QoL for the child or parent was shown. However, at one site, mean A1c in the year post-intervention declined by 0.059% more per month for intervention group teens than for those receiving usual care (p=0.02). At this same site, mean parent QoL increased by 0.61 points per month more during the intervention for parents of intervention group children than parents of those receiving usual care (p=0.03).

Conclusions: Findings can inform healthcare organizations’ decisions about ways to best deliver diabetes self-management resources.

Supported By: American Diabetes Association (11-17-CT-41 to L.R.L), (1-17-JDF-008 to S.A.W.G.); Novo Nordisk; National Institute of Diabetes and Digestive and Kidney Diseases (R01DK104942, P30DK020595, K23DK094866); National Center for Advancing Translational Sciences (UL1TR000427); Kovler Family Foundation
Socioeconomic Disparities in Outpatient Diabetes Care Patterns for Young Adults with Type 1 Diabetes

SHIVANI AGARWAL, HANNAH L. VIROSLAV, JACK N. EIEL, JUDITH A. LONG, Philadelphia, PA; Dallas, TX

Background: Few young adults (YA) with type 1 diabetes (T1D) achieve national glycemic targets, and even fewer of low socioeconomic status (SES) meet these goals. Inconsistent clinic attendance is thought to contribute to this disparity in glycemic control but has not been studied.

Methods: We evaluated clinic attendance in YA with T1D, 18-25 years, seen in a young adult diabetes clinic. We extracted data from medical charts and used insurance status to identify low and higher SES YA, comparing individuals with federal/state-sponsored (public) insurance to commercial (private) insurance. Glycemic control was defined as the difference between the last documented A1c and the baseline first appointment A1c. There were 2 outcomes representing inconsistent attendance: 1) missing ≥2 scheduled quarterly visit per year and 2) gap in care >6 months. We used multilevel mixed effects linear and logistic regression models to examine relationships between insurance status, inconsistent attendance, and glycemic control, adjusting for demographic, clinical, social, and health system factors.

Results: 312 YA were seen in the clinic (mean age 23.5 years; totaling 2376 care visits. Forty-six percent (n=147) had public insurance. Publicly insured YA were more frequently black (42% vs. 11%, p<0.001) and in worse glycemic control (mean baseline A1c 9.9% vs. 8.1%, p<0.001). In multivariate analyses, compared to privately insured YA, publicly insured were 50% more likely to miss a quarterly appointment (OR=1.56, p<0.005) and 96% more likely to have a gap in care >6 months (OR 1.96, p=0.008). In addition, missed appointments worsened glycemic control from baseline (A1c +0.57%, p=0.001).

Conclusions: Low SES YA with T1D are a particularly high-risk subset who are more likely to miss appointments and have gaps in care, which is associated with worse glycemic control. Our results highlight the need to refocus on improving follow-up rates in vulnerable populations to address disparities in glycemic outcomes.

Supported By: Penn Rodebaugh Diabetes Center

Type 1 Diabetes Transition Program at a Children’s Hospital—Lessons Learned and Future Directions

HOLLY CURNWELL, SEVKET YIGIT, RADHAKA PURUSHOTHAMAN, Portland, OR

Background: Transitioning a child with type 1 diabetes (T1DM) poses many challenges. Structured programs decrease loss to follow-up and hospitalization rates. We created a transition program, modeled after the Sweet transition program (Queensland, Australia) and monitored the outcomes.

Methods: The program was implemented in April 2015. Steps included: Assessing T1DM knowledge at age 12, education based on need/age, providing an adult provider list, sending providers a clinical summary and maintaining a referral registry. The program was revised in October 2016, now included follow-up by a coordinator and a patient survey evaluating the program.

Results: There was increased attendance to education sessions. Transition to adult care within 6 months also improved. No one was lost to follow-up. We received useful feedback from patients about the program.

Lessons learned:
1. The ADA guidelines need to be customized based on available resources.
2. Starting at age 12 helps improve transition.
3. A transition registry and coordinator are important.

Future directions:
1. Provide subjective assessments for patients to gauge their T1DM knowledge.
2. Collaborate with adult providers via combined clinic.

Analysis of the Social Network and Physical Activity Performed as Perceived by Young Patients with Type 1 Diabetes

PIERGIORGIO FRANCA, BARBARA PICCINI, UGO SANTOSUSOSSO, GIULIA IANNONE, LAURA CAPIRCHIO, ALESSANDRO VITTORI, MASSIMO GALISANO, SONIA TOMI, Florence, Italy

In addition to the knowledge of the daily physical activity performed (PAP), the analysis of the social network perceived directly by the same young patients with type 1 diabetes mellitus (T1DM) could provide useful information to manage their diabetes. The aim of this study was to evaluate the presence of a relationship between the patients’ social networks, the PAP and the metabolic control maintained in young subjects with T1DM. Interviews were conducted in 16 subjects with T1DM (males/females: 7/9), mean age 15.5±0.8 years; duration of diabetes 6.6±4.9 years; mean HbA1c (at baseline) 7.3±1.7% (year before) 7.3±1.6%, body mass index (BMI) 21.6±2.9 kg/m² and in 12 age and BMI matched healthy control subjects. Participants were asked to fill in an egocentric social network map, which was divided into 5 areas: family, school, health care, leisure and sport activities. Other. It was assigned a value ranging from 0 (none) to 5 (maximum) to define importance and frequency of the relationships reported. The PAP was evaluated by the Physical Activity Questionnaire for Children (PAQ-C) and Adolescents (PAQ-A).

While the analysis of the PAP and of the glycemic control maintained did not show any correlation with the other parameters, the analysis of the network showed that the frequency reported on the area of leisure and sport activities was significantly lower in the patient group in comparison to controls (4.2±1.8 vs. 3.1±1.0, p<0.05). From the analysis of the two groups, the young patients investigated reported to attend significantly fewer sports clubs (2.3±0.6 vs. 4.2±1.0, p=0.01) and have less contact with teammates (2.6±1.5 vs. 4.2±1.3, p<0.05). However, they mainly attend hospital (2.0±1.1 vs. 0.6±0.7; p<0.001) and friendly societies (1.5±1.1 vs. 0.1±0.4; p<0.001). The results of this pilot study showed that the analysis of patients’ social networks could contribute to improving knowledge and therefore providing additional information useful for better management of these patients.
This study presents data on MVPA in children and adolescents with T1D over a long duration using objectively measured physical activity. Our results suggest that sex is an important factor associated with MVPA and that over 75% of children in this population do not regularly meet the ADA MVPA recommendations.

**1385-P**  
Relationship between Mean Glucose and A1c by Pubertal Stage in Youth with Type 1 Diabetes (T1D)  
JIA ZHU, LISA VOLKENING, MICHELLE KATZ, LORI M. LAFFEL, BOSTON, MA  
Background: Correlations between mean glucose and A1c vary among persons with T1D, with weaker associations in youth vs. adults. We investigated the relationships between mean glucose assessed by continuous glucose monitoring (CGM) and A1c according to pubertal stage in youth with T1D.  
Methods: Mean glucose and percent of time in various glucose ranges (<70, 70-180, >250 mg/dL) were calculated using CGM data from the 4 weeks before A1c measurement in 107 youth, ages 8-17, with T1D. Glucose data were compared by pubertal stage (pre-pubertal: Tanner (T) 1, pubertal: T2-4, post-pubertal: T5) and A1c categories (<7.5%, 7.5-8.4%, ≥8.5%).  
Results: Mean (±SD) ages for the pre-pubertal (64% male), pubertal (56% male), and post-pubertal (32% male) groups were 10.1±3.2, 12.9±1.4, and 15.9±1.6 years, respectively. For the entire sample, CGM data (196±29 mg/dL) and A1c (7.8±0.8%) were highly correlated (r=−.71, p<.001). Overall and among youth with A1c ≥7.5% vs. A1c <7.5%, there were no differences in mean glucose, A1c, or percent time in various glucose ranges according to pubertal stage (Table).  
Conclusions: Pre-pubertal youth appear to have higher mean glucose than reflected by their A1c, particularly for those achieving A1c ≥7.5%, suggesting greater glycemic excursions in young children. Ideally, A1c should be interpreted in association with CGM data, particularly in young children, in efforts to optimize glycemia.

<table>
<thead>
<tr>
<th>Pubertal Stage</th>
<th>Pre-pubertal</th>
<th>Pubertal</th>
<th>Post-pubertal</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All youth</td>
<td>n=28</td>
<td>n=45</td>
<td>n=34</td>
<td></td>
</tr>
<tr>
<td>Mean glucose (mg/dL)</td>
<td>202±23</td>
<td>199±21</td>
<td>193±35</td>
<td>0.5</td>
</tr>
<tr>
<td>A1c (%)</td>
<td>7.8±0.8</td>
<td>7.9±0.8</td>
<td>7.8±1.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td>0.62</td>
<td>0.71</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>% time &lt;70 mg/dL</td>
<td>31±3</td>
<td>31±2</td>
<td>32±2</td>
<td>0.6</td>
</tr>
<tr>
<td>% time 70-180 mg/dL</td>
<td>43±8</td>
<td>46±12</td>
<td>46±15</td>
<td>0.6</td>
</tr>
<tr>
<td>% time &gt;250 mg/dL</td>
<td>28±10</td>
<td>24±11</td>
<td>24±14</td>
<td>0.4</td>
</tr>
<tr>
<td>Youth with A1c ≥7.5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean glucose (mg/dL)</td>
<td>308±18</td>
<td>271±13</td>
<td>169±23</td>
<td>0.049</td>
</tr>
<tr>
<td>A1c (%)</td>
<td>7.1±0.6</td>
<td>7.0±0.3</td>
<td>7.0±0.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td>0.15</td>
<td>0.46</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>% time &gt;70 mg/dL</td>
<td>42±6</td>
<td>31±2</td>
<td>32±2</td>
<td>0.7</td>
</tr>
<tr>
<td>% time 70-180 mg/dL</td>
<td>46±8</td>
<td>58±12</td>
<td>58±12</td>
<td>0.6</td>
</tr>
<tr>
<td>% time &gt;250 mg/dL</td>
<td>22±7</td>
<td>14±6</td>
<td>14±7</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**1386-P**  
Effect of Significant Family Life Events in the First Year of Type 1 Diabetes (T1D)  
KELLY R. STANEK, SHIDEH MAJIDI, ERIN M. YOUNSKIN, AMY NOSER, MARK A. CLEMENTS, SUSANNA R. PATTON, Aurora, CO; Lawrence, KS; Kansas City, MO; Kansas City, KS  
Objective: Examine the impact of stressful life events on families in the first year after diagnosis of T1D in a young child using a novel methods design.  
Methods: In a prospective study of 5-9-year-olds new to T1D (mean age 7.4±1.3 years, T1D duration 4.7±3.3 months), we measured A1c, changes in family health, marital status, coping, and income every 3 months up to 12 months post-pubertal-based on sex.  
Results: Of 135 families, 40 reported job/income changes (11 promoted, 20 changed job, 7 quit job, 2 lost job), 4 marital changes (2 divorces, 1 separation, 1 spouse death), and 42 health changes (78.6% family member health, 21.4% child). Of those, 4 family members were also diagnosed with T1D and 3 youth were diagnosed with an autoimmune disorder in the 12 month follow-up. Income decrease at any time point in first 12 months correlated with health change (r=0.142, p=0.048) and marital status change (r=0.169, p=0.049) at any time point in the first 12 months, while baseline Avoidance Coping correlated with future income decrease (r=0.169, p=0.03). There was a cross-sectional association between A1c and income decrease at time point 4, corresponding to ~1 year post-T1D diagnosis (Table).  
Conclusions: Families can experience significant concurrent life stressors during the first year of T1D. Future research should explore if these events have a direct effect on T1D management and long-term glycemic control.

**1387-P**  
Higher Weekly Physical Activity in T1D Pediatric Patients Is Associated with Improved Target Glucose Levels—Findings from Six Months of Fitbit-Monitored Activity  
TIMOTHY L. BARNES, DAVID A. WATSON, LAURA M. GANDRUD, Minneapolis, MN; Saint Paul, MN  
Physical activity (PA) in T1D patients has been linked to improved cardiovascular and psychosocial health. Glycemic control has been reported as a benefit of PA, but it remains difficult to assess ‘real-life’ PA in T1D pediatric patients.  
In a novel study, we examined the relationship between weekly Fitbit-measured PA and blood glucose (BG) in 105 patients over 6 months. BG was measured via home meters. Using generalized linear mixed effects regression we examined the association between weekly PA measures—steps and hours of moderate to vigorous PA (MVPA)—and weekly summaries of BG levels in, below, and above target range (70-140 mg/dL).  
On average, patients took 56K steps/week and had a weekly BG measurement of 221 mg/dL. In regression models, as PA increased, patients tended to have significantly lower mean BG levels and more BG measurements in target range. Thus, an increase in 10K steps was associated with a 3.1 mg/dL drop in BG levels and a 6% increase in the odds of a target range BG (Table). An additional hour of MVPA was associated with a 2.3 mg/dL drop in BG levels and a 4% increase in the odds of a target BG measurement. PA was also associated with being below the target range.  
This study provides evidence for the positive effects of PA on BG among pediatric T1D patients, providing a further impetus for promoting PA among this population.

Table: Generalized Linear Mixed Effects Regression Models Examining Relationship between Weekly PA and BG Levels1 (n=105).  
<table>
<thead>
<tr>
<th>BG Measurement</th>
<th>Average % Normal</th>
<th>% Between 70-140 mg/dL</th>
<th>% Below 70 mg/dL</th>
<th>% Above 140 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>p&lt;0.05% CI2</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Steps (per 10K)</td>
<td>-3.1</td>
<td>-1.02 (1.15, 0.97)</td>
<td>1.03 (1.08, 1.08)</td>
<td>0.96 (0.95, 0.99)</td>
</tr>
<tr>
<td>Hours of MVPA</td>
<td>-2.3</td>
<td>-1.01 (1.01, 1.01)</td>
<td>1.00 (1.00, 1.00)</td>
<td>0.98 (0.95, 0.99)</td>
</tr>
</tbody>
</table>

1Adjusted for baseline HbA1c, baseline BMI (z-score), age group, sex, treatment group. 2 Beta is the fixed effects linear regression coefficient for the specified PA measurement. OR is the odds ratio of the indicated event for each unit increase of PA.

**1388-P**  
A Paradoxical Relationship between Physical Activity and HbA1c in Pediatric T1D Patients  
DAVID A. WATSON, TIMOTHY L. BARNES, LAURA M. GANDRUD, Minneapolis, MN; Saint Paul, MN  
Regular physical activity (PA) has been found to contribute to lower HbA1c in T1D pediatric populations, but this relationship is not conclusive. In a recent study, we examined associations between PA and HbA1c over 6 months in 105 T1D pediatric patients. PA was measured with Fitbit moni-
Five-Year Experience with Telemedicine Clinics for Youth with Type 1 Diabetes (T1D)

R. PAUL WADWA, JOHN STACY, TYLER REZNICK-LIPNA, ROBERT H. SLOVER, JOHN F. THOMAS IV, Aurora, CO; Grand Forks, ND

Poor access to specialty care is a problem for youth with T1D in rural America, where 79% of children live over 20 miles from a pediatric endocrinologist. Rural families are less likely to have adequate T1D follow-up per ADA guidelines. Telemedicine may mitigate such issues. Since 2012, the Barbara Davis Center for Diabetes telemedicine program has provided care for over 290 pediatric T1D patients in rural Wyoming and Colorado via real-time, encrypted videoconferencing. This study sought to determine how increased access to specialty care via telemedicine affects glycemic control over a 3 to 5 year follow-up period. Glycemic control was analyzed for 21 patients with at least 3 years follow-up since initial use of telemedicine. Data were analyzed by age group (< 12 years [pre-pubertal, n=13] vs. ≥12 years [post-pubertal, n=8]) and treatment method at baseline (insulin pump, n=8 vs. multiple daily injections (MDI), n=13). Mean T1D duration at baseline was 4.1 ± 3.5 years and mean follow-up time was 4.1 ± 0.6 years. Mean change in A1C was 0.0 ± 0.2% (p=0.96 for baseline vs. follow-up A1C). Median (interquartile range) (IQR) A1C at baseline and at follow-up were 9.2 (8.2, 11.0)% and 9.0 (8.5, 10.1)% respectively. One third of patients had a clinically significant increase in A1C of more than 0.5%, a third had a decrease of more than 0.5% and a third had no change in A1C. The post-pubertal group showed worse change in glycemic control compared to the pre-pubertal group (mean A1C change 0.2 ± 3.0 vs. -0.1 ± 1.3% respectively (p=0.78)). Patients on MDI at baseline showed mean A1C change of -0.5 ± 1.4% compared to a mean A1C change for patients on insulin pumps of 0.9 ± 2.7% (p=0.21). Of 13 MDI patients, 7 transitioned to insulin pump use during follow-up. Overall, glycemic control was no worse and pump use increased with 5 years of telemedicine clinics for T1D youth. While further work is needed to improve overall glycemic control, use of telemedicine reduces barriers and improves access to T1D specialty care for rural families.

Sustained CGM Use in Low Income Youth following Insurance Coverage

JOHN F. THOMAS IV, BRUCE BUCKINGHAM, DARRELL WILSON, DAVID M. MAAHS, Stanford, CA; Paso Alto, CA

California Children’s Services (CCS) is a supplemental state medical insurance for low income children with chronic medical conditions. Until June 2016, continuous glucose monitors (CGM) were rarely covered by CCS for children with type 1 diabetes (T1D). Current CCS criteria for CGM includes: checking blood sugar 4 times/day and concerns that interfere with T1D management (such as fear of hypoglycemia). Ongoing approval requires CGM use for 5/7 days/week.

We evaluated 6 months of CGM use by the first 41 children approved by CCS attending our clinics (ages: 11.1 ± 4.7 years [range 3-21 years], T1D duration= 4.8 ± 3.7 years, 59% male, 86% on pumps, 63% ethnic minorities and 15% non-English speakers). Most patients used the Dexcom receiver (73%). Thirty-three (81%) remained on CGM for ≥6 months. Of the 8 who stopped, 2 were due to lapses in insurance coverage. The other 6 stopped due to personal preference (5 within 3 months). All who stopped CGM use were English speakers. Among those who continued CGM with complete data (n=29, 71%), the mean percentage time worn at 6 months was 97±6% based on review of the CGM download. HbA1c remained stable over 6 months of CGM use (8.2±1.2%). Blinded CGM use was not available prior to initiation of personal CGM, so we cannot assess if hypoglycemia decreased. However, many of these children with CCS started CGM due to hypoglycemia and/or fear of hypoglycemia. Time in hypoglycemia as low as 6 months (4.3±0.8%). The number of fingersticks remained stable with 6.3/d at initiation and 5.6/d at 6 months.

Our clinic data from the first 41 CCS patients approved for CGM demonstrates sustained CGM use for 6 months, even among non-English speakers. In this initial chart review, the incidence of hypoglycemia in low while on CGM. These data on sustained usability of CGM support CCS coverage of CGM. Given FDA approval of CGM use for insulin dosing decisions, expansion of CCS coverage of CGM should be considered to improve bolus adherence. Further studies are needed to promote improved clinical use and outcomes with CGM in this population.

Parental Hypoglycemia Fear and Adoption of Pump Therapy in Youth with New-Onset Type 1 Diabetes (T1D)

ERIN M. YOUNGKIN, SHIDEH MAJIDI, AMY NOSER, KELLY R. STANEK, JONAH-THAN H. FINCH, MARK A. CLEMENTS, SUSANA R. PATTON, Aurora, CO; Lawrence, KS; Kansas City, KS; Kansas City, MO

Objective: Hypoglycemia Fear (FH) is common in parents of young children with T1D and related to poor child glycemic control. We explored if T1D device adoption near onset relates to parental FH.

Methods: In a prospective study of 5-9 year-olds with new onset T1D (mean age 7.4±1.3 years, mean T1D duration 4.6±3.3 months), parents completed the FH Survey at baseline (T1) and 6 (T3) and 12 (T5) months post-baseline. We recorded pump start dates for youth during the same 12 months.

Results: Between T1 and T3, 44 youth (45%) initiated pump therapy. Between T3 and T5, 12 (13%) started a pump. Forty-one youth never started a pump (42%). Despite pump status, parents reported moderate FH Worry at T1 (54±3.0) which decreased between T1 and T3 (40±1.3, p=0.052) and plateaued between T3 and T5 (38±4.2, p=0.45). There was no difference in T1 FH Worry among the 44 parents of youth who started a pump between T1 and T3 and those not on a pump. At T3, FH Worry trended higher in the 12 parents whose child started a pump between T3 and T5 than the 85 parents of youth either already on a pump or not on one (p=0.059). At T5, the 12 parents whose child started a pump between T3 and T5 reported significantly higher FH Worry than the other parents (p=0.048).

Conclusions: Parents of 5-9 year-olds with new onset T1D report moderate FH in the first year of T1D. Our results suggest that initiating pump therapy may not reduce parental FH.
Clinical Diabetes/POSTERS

Control and Self-Care Behavior in Adolescents with Type 1 Diabetes

LORI M. LAFFEL, Boston MA, CA, MI

Inhibition of Nox-1 Activity Attenuates Diabetic Ketoacidosis-Induced Blood Brain Barrier Permeability and Edema Formation

GABRIELA MARTINEZ-REVOLLAR, Ann Arbor, MI

Diabetic ketoacidosis (DKA) is a condition characterized by hyperglycemia and high ketone bodies production conducting to acidosis. DKA is highly prevalent in pediatric patients. Approximately 0.5%-1% of these children develop cerebral edema, with a mortality rate of 20-30%. Our research examined the effects of DKA in Blood Brain Barrier (BBB) permeability using Ins2(-/-) mice as a DKA model. Using magnetic resonance (MR)-based detection of the contrast agent gadolinium diethylenetriaminepenta-acetic acid (Gd-DTPA) we observed BBB permeability and fluid accumulation in the brain, during DKA episodes from day 1 to 5. Our data indicated that increased BBB permeability was present in the thalamus, partial cortex and basal forebrain. Furthermore, the analysis of the morphological and functional changes of BBB under DKA conditions both in vitro and in vivo showed alterations in TJ proteins, manifested as a slight alteration in z0-1 and Claudin-5 expression which could represent the ground for BBB leakage. We have further identified that DKA promotes the high production of ROS due to Nox-1 activation, leading to actin reorganization, the subsequent TJ disorganization and increased BBB permeability. The inhibition of Nox-1 activity via Nox-1 inhibitor ML-17 improved the BBB integrity and reduced leakage. Collectively, these studies will provide new information related to novel therapeutic strategies to prevent or reverse vascular hyperpermeability in DKA.

1393-P

Establishing a Clinically Meaningful Cut-Point for the PAID-PR (Problem Areas in Diabetes-Parent Revised) Survey

Liane J. Tinsley, Persis V. Commissariat, Lisa Volkeling, Barbara Anderson, Michelle Katz, Lori M. Laffel, Boston, MA, Charlottesville, VA

The 18-item PAID-PR has shown construct validity with BGM frequency, A1c, and measures of diabetes-specific family conflict (DSFC) and general quality of life (Qol). Higher PAID-PR scores (range 0-100) indicate more diabetes distress. We applied a standard approach to identify a meaningful cut-point: scores ≥75th percentile of the distribution of PAID-PR scores obtained from 2 large clinic samples. Cutoff scores was confirmed by convergent validity, including demographics, diabetes data from youth, and parent reported psychosocial measures (DSFC and Qol).

The sample included 527 parents of youth with T1D. Youth (50% male, 84% white) were aged (M±SD) 9.6±3.6 years; 86% were from 2-parent families. Youths checked BG 4.6±6.2 x/day; A1c was 8.4±1.1% and 69% were pump-treated. PAID-PR score was 33.4±18.5 (range 0-92, IQR 31-58). Analyses determined a cut-point of 56. Youths whose parents scored in the upper quartile vs. lower 3 quartiles were similar with respect to sex and racial distributions, age, percent 2-parent families, T1D duration, and BGM checks/day. There were significant differences in A1c (8.6±1.2 vs. 8.3±1.1%) and pump use (60 vs. 71%) (p<.01 for both) between youth whose parents were in the upper vs. lower 3 quartiles.
of the PAID-PR. Parents in the upper quartile vs. lower 3 quartiles reported more DSF and poorer youth QoL (p<0.001 for both).

As youth-onset T1D may engender diabetes distress in females, pediatric diabetes teams recognize the need to identify parents experiencing extreme symptoms. A cut-point of 56 on the PAID-PR appears to identify females in need of additional medical and psychological support in order to improve biomedical and psychosocial outcomes.

Supported By: National Institutes of Health (R01DK083349, T32DK007260, K12DK016072, K23HL125876, P30DK066138)

1396-P

Racial Ethnic Disparities in Diabetes Youth Participating in Diabetes Summer Camps

JESSICA M. VALENZUELA, MEGAN T. MARTIN, SAM RECORDS, KELLY O’NEAL, KELLY MUELLER, RISA M. WOLF, Davie, FL, Arlington, VA, Baltimore, MD

Background: Diabetes camps are beneficial for campers, including increases in diabetes knowledge, glycemic control and psychological functioning. Racial/ethnic minority youth are likely to have poorer disease management and glycemic control, more complications, and are often managed with less intensive, less technologically advanced regimens. We hypothesized that racial/ethnic minority youth with type 1 diabetes (T1D) would have reduced participation in diabetes summer camps.

Methods: We reviewed de-identified data from 5033 campers with T1D who participated in a network of 46 ADA-affiliated summer camps during the 2017 season. We performed t-tests and chi-square analysis to analyze the demographic characteristics of white vs. non-white campers.

Results: Campers with T1D came from all over the U.S. (49 states), 68.6% were return campers, 55% were female, ages ranging from 4-18 (m=11.7 ± 2.8). Of campers, 73.2% were on insulin pump regimens. Camps cost $0 to $1400 (Day Camps M=$158.83 ± $103.69, Residential Camps M=$622.73 ± $274.24). Campers identified as Caucasian (83.9%), black (4.8%), Hispanic (3.9%), Asian/Pacific Islander (2.7%), and Multiracial (3.9%). We compared ethnicity data to the 2009 SEARCH data from children and adolescents where T1D prevalence was 72% in Caucasians, 9% black, 15% Hispanic and 2% Asian/Pacific Islander. Camper demographics were significantly different than the general population of children with T1D (p<0.001). Racial/ethnic minority status was associated with type of camp attended (day vs. residential), and minority campers were less likely to be on insulin pump therapy.

Conclusions: Children of ethnic minorities with diabetes are underrepresented in diabetes camps nationwide compared to the prevalence of diabetes in each minority group as described by the SEARCH study. This highlights the need to assess barriers to camp attendance in these communities and to design outreach programs to increase minority youth participation in the diabetes camp experience.

1397-P

Effects of Modified Lipoproteins on Human Trophoblast Cells—A Role in Preeclampsia in Pregnancies Complicated by Diabetes

REBECCA H. MCLEESE, JIAWU ZHAO, JEREMY YU, DEREK BRAZIL, TIMOTHY LYONS, Charleston, SC, Belfast, United Kingdom

Preeclampsia (PE) complicates 2-8% of pregnancies worldwide. In women with diabetes, the risk for PE is substantially increased by approximately 4 fold. Evidence indicates that an increased release of two anti-angiogenic factors, soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng) from placental trophoblasts into the maternal circulation promotes endothelial dysfunction associated with PE. In this study, we investigated sFlt-1 and sEng release from the human placental trophoblast cell line, HTR8/SVneo, in response to modified lipoproteins and/or elevated glucose. HTR8/SVneo cells were exposed to native low-density lipoprotein (N-LDL) vs. ‘highly oxidized’ ‘glycated’ LDL (HOG-LDL) (50 µg protein/ml) for 24h, with and without pre-treatment with 30mM glucose for 72h. The mRNA expressions of sFlt-1 and sEng in cell supernatant were measured by RT-PCR. Compared with N-LDL, HOG-LDL increased the mRNA expression of sFlt-1 and sEng by 1.5 fold and 1.8 fold, respectively, compared to HOG-LDL treatment alone (p<0.05 for both). Exposure of trophoblasts to modified lipoproteins (which accumulate in the tissues of patients with diabetes due to vascular leakage) may contribute to the development of PE in diabetes, which is amplified by the presence of high glucose. These findings may explain, in part, the high risk of PE in women with diabetes.

1398-P

Olive Oil Supplementation Reduces Proinflammatory Markers in the Placenta in a GDM Rat Model Induced by Intratracheal Programming

DALMIRIO L. GOMEZ BIBOT, EVANGELINA CAPOBIANCO, CECILIA P. LEVIEUX, DIANA FORNES, ALICIA JAWERBAUM, Buenos Aires, Argentina

Gestational diabetes (GDM) is associated with an increased proinflammatory state in the placenta, which affects fetal development and offspring’s health. We have previously found that gestational mild diabetes in Wistar rats (F0) programs GDM in the adult female offspring (F1). Our aim was to treat this F1 with a diet enriched in olive oil to address the ability of this treatment to prevent both excessive matrix metalloproteinase 2 (MMP2) and connective tissue growth factor (CTGF) levels and reduced PPARgamma levels in the placenta, associated to the preeclamptic state.

Methods: Mild pregestational diabetes was induced by neonatal streptozotocin administration (80mg/kg). Pregestational diabetic female rats and control females were mated with control males, and their adult female offspring (F1) mated with control males. F1 rats were fed a standard diet or a diet supplemented with 8% olive oil during pregnancy. On day 21 of pregnancy, maternal and placental plasma were evaluated.

Results: The olive oil treatment in the F1 pregnancy did not prevent maternal or fetal hyperglycemia in the pregnant offspring of pregestational diabetic rats. Maternal supplementation with olive oil reduced maternal triglyceridemia in GDM rats (21%, p<0.05) compared to GDM rats fed the standard diet. The placenta from GDM rats showed increased MMP2 and CTGF levels compared to controls (26%, p<0.05 and 37%, p<0.001, respectively). Alterations prevented by the maternal treatment with olive oil. PPARgamma levels were reduced in GDM placentas treated and untreated with the olive-oil diet compared to controls (32% and 35% respectively, p<0.05).

Conclusions: Although the maternal diet enriched in olive oil was not able to prevent GDM induction or reduced PPARgamma placental levels, it prevented maternal hypertriglyceridemia and exerted anti-inflammatory effects in the placenta from GDM rats, thus likely benefiting the fetal development.

Supported By: Consejo Nacional de Investigaciones Científicas y Técnicas de Argentina; Agencia Nacional de Promoción Científica y Tecnológica

PKC Modulates sFlt1 Production by Human Placental Trophoblasts in Response to Oxidized LDL

REBECCA P. CHOW, JIAWU ZHAO, JEREMY YU, CHARLOTTE, SC, Belfast, United Kingdom

Preeclampsia (PE) is a leading cause of maternal and perinatal mortality and morbidity, and its prevalence is 4 fold higher in women with diabetes than those without: the underlying mechanism is unclear. The anti-angiogenic factor soluble fms-like tyrosine kinase-1 (sFlt1) plays a key role in PE pathogenesis. Evidence suggests that PKC activation, which is associated with the development of diabetic vascular complications, may mediate the enhanced sFlt1 release in non-trophoblast cells. We aimed to determine the role of PKC in the regulation of sFlt1 expression in placental trophoblasts, and whether diabetic conditions upregulate sFlt1 expression via the PKC pathway. Human trophoblasts HTR8/SVneo were treated in three separate experiments with PKC activator phorbol-12-myristate-13-acetate (PMA), or diabetes stimuli ‘heavily oxidized’, glycated low-density lipoproteins (HOG-LDL) vs. native LDL ± high glucose. These findings may explain, in part, the high risk of PE in women with diabetes.

ADA-Supported Research

Moderated Poster Discussion
lipopolysaccharides may promote PE development in women with diabetes, at least in part via PKC-mediated upregulation and release of sFlt1. These findings provide new insights into disease mechanisms, and may lead to new targets for prevention and treatment of PE.

Pancreatic β-Cell Mass Is Determined by β-Cell Size after Parturition in Mice

MASAYA TAKAHASHI, TAKESHI MIYATSUKA, MIWA HIMURO, LIKA SUZUKI, MASAKI MIURA, TAKEHIRO KATAKURA, YUYA NISHIDA, ATSUO ITAKURA, SATORU TAKEDA, HIROAKA WATADA, Tokyo, Japan

During pregnancy, β-cell mass is increased through β-cell hypertrophy and proliferation to adapt to insulin resistance. While β-cell mass is known to return toward non-pregnant levels after parturition, the cellular mechanisms by which β-cell mass is regulated during this period remains unclear.

To address this issue in mice, we first quantified β-cell mass throughout the perinatal period using C57BL/6J female mice, and found that increased β-cell mass at gestational day 18 (G18) was significantly reduced at postpartum days 7 (P7), to comparable level with that in age-matched, non-pregnant (NP) female mice. Co-immunostaining for insulin and E-cadherin, which enabled us to precisely measure individual β-cell size, revealed that the mean β-cell size was significantly increased during perinatal periods at G18 and P1 than during non-pregnant state, and robustly decreased at P7. Intriguingly, the mean β-cell size at P7 was slightly but significantly smaller than that in the non-pregnant mice, and then returned to the non-pregnant levels until P21. On the other hand, quantification of apoptosis by TUNEL assay demonstrated that there was no significant difference in the number of apoptotic cells among the groups. To further investigate the contribution of dedifferentiation or transdifferentiation in reduced β-cell mass after parturition, we performed genetic lineage tracing using Ins1-Cre; ROSA26lacZ
gene. We previously found that β-cell mass is increased in the fetal circulation during diabetic pregnancy and that this potentially reflects the response of monocytes/macrophages to hyperglycemia and metabolic stresses associated with diabetic pregnancy. In addition, human resistin has the capacity to decrease mitochondrial biogenesis by affecting the epigenetic regulation of PGC-1α expression. Thus, increased exposure to resistin may contribute to mitochondrial dysfunction and long-term aberrant energy metabolism characteristic of the offspring of diabetic pregnancies.

Supported By: American Diabetes Association (7-10-CT-09 to S.J.), National Institutes of Health (R01DK089034 to S.C.), P20MD000528 (to T.L.) Presbyterian Health Foundation (to S.J.)

Fetal Brain Activity in Pregnancy of Women with Type 1 Diabetes Mellitus

ELLEN FEHLERT, FRANZISKA SCHLEGER, KATARZYNA LINDER, MARTIN HENI, HANS-ULRICH HAERING, HUBERT PREISS, ANDREAS FRITSCHIE, Tübingen, Germany

We previously found gestational diabetes mellitus (GDM) to be associated with prolonged fetal auditory evoked brain responses (fAER) in fetal magnetoencephalography (fMEG). We asked whether maternal type 1 diabetes mellitus (T1D) may alter fetal brain activity.

Pregnant women with well-controlled T1D (n=4, A1c <6.5%) were measured with fMEG before and 60 min. after a defined meal. Latencies of fAER were analyzed. We obtained two control groups of women with GDM (n=8) and normal glucose tolerance (NGT, n=8) out of 151 pregnant women with fAER. The groups were carefully matched by gestational age and pre-pregnancy maternal BMI.

ANOVA showed a main effect of group on the change in latency between baseline and postprandial state (F[2]=4.14, p=0.034). In accordance with our previous results, in post-hoc tests the change of latency was smaller in the GDM than the NGT group (p=0.032). No difference was found in the change of latency between T1D and NGT or GDM. The number of fetuses showing faster fAER postprandially is higher in T1D and NGT than in GDM. For details see Table.

To our knowledge, this is the first study investigating fAER in maternal T1D. In contrast to GDM, our preliminary results indicate that well-controlled maternal T1D does not impair fetal postprandial brain activity. These findings may indicate that fAER are associated with metabolic features primarily present in maternal insulin resistance.

Table. Latency of Fetal Auditory Evoked Responses in MS (means ±SD).

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Baseline (0 min)</th>
<th>Postprandial (60 min)</th>
<th>Change</th>
<th>Number of fetuses with speeding up of fAER</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGT</td>
<td>8</td>
<td>277 (±103)</td>
<td>204 (±89)</td>
<td>-72 (±81)</td>
<td>7/8 (88%)</td>
</tr>
<tr>
<td>T1D</td>
<td>4</td>
<td>257 (±57)</td>
<td>262 (±151)</td>
<td>+6 (±119)</td>
<td>3/4 (75%)</td>
</tr>
<tr>
<td>GDM</td>
<td>8</td>
<td>222 (±82)</td>
<td>288 (±157)</td>
<td>+65 (±100)</td>
<td>3/8 (38%)</td>
</tr>
</tbody>
</table>

Family History of Diabetes Delays Fetal Brain Activity

FRANZISKA SCHLEGER, LAURA WALTER, MARTIN HENI, SARA Y. BRUCKER, HANS-ULRICH HAERING, ANDREAS FRITSCHIE, HUBERT PREISS, Tübingen, Germany

Introduction: We have previously shown that fetuses of mothers with gestational diabetes mellitus (GDM) and insulin resistance exhibit a prolongation of fetal auditory evoked brain responses (fAER) compared to fetuses of normal glucose tolerant (NGT) women during an oral glucose tolerance test (OGTT). This implies that maternal metabolism may program the fetal brain. We asked whether a positive family history of type 2 diabetes (FHD) without metabolic programming also impacts fetal brain activity. We therefore investigated brain activity in fetuses of NGT mothers with positive FHD.

Methods: A 75g OGTT was administered to healthy pregnant women. Glucose and insulin levels were measured after 0, 60 and 120 minutes. Each blood extraction was preceded by magnetoencephalographic recordings of fAER. From a group of 151 participants, a sub-sample of 53 women, 38 with a negative and 15 with a positive FHD (at least one first- or second-degree relative) was selected based on the following inclusion criteria: no GDM, BMI 18.5-30 kg/m², no preterm birth, no change in fetal position, at least two blood samples with detectable fetal responses.

Results: There were no significant differences in age, BMI at delivery, weight gain during pregnancy and gestational age between the groups. Maternal glucose levels and insulin sensitivity determined by glucose and insulin measurements during the OGTT were not significantly different. Manova with gestational age as covariate showed a significant interaction between measurement timepoint and FHD on fAER latency (F[2]=4.96, p=0.003). Fetuses of mothers with positive FHD had a prolonged fAER (273±109ms) compared to fetuses of mothers with negative FHD (218±67ms) at 60 minutes during the OGTT (F[1]=5.21, p=0.027).

Discussion: In addition to the previously shown influence of maternal metabolism on fetal brain activity, a positive maternal FHD also appears to delay fetal brain activity. This can be due to the genetic or environmental influence which is linked to a positive FHD.

Supported By: Deutsches Zentrum für Diabetes Forschung (0160925)
High Maternal DHA Levels in Hawaiian Women Decrease Insulin Resistance

FERNANDA ALVARADO, PAI-JONG TSAI, JUDI MINIMUM, PATRICK CATALANO, PERRIE O’TIERNEY-ISHIN, Cleveland, OH, Honolulu, HI

Obesity prevalence during pregnancy (PG), a significant risk factor for metabolic inflammation and subsequent increase in insulin resistance (IR), has increased ~35% in the last 20 years. Offspring of obese (OB) women are at a higher risk of metabolic dysfunction. Omega-3 fatty acids such as DHA have been shown to decrease IR in animals, though the effects of DHA in PG women are unclear. We hypothesize that high plasma DHA levels are associated with lower IR in PG women in an environment of high omega-3 intake (Hawaii), but differ in metabolic effect in OB vs. lean (LN) women. We evaluated 54 healthy, normal glucose tolerant women and their offspring at term elective C-section in Honolulu. We grouped subjects according to their pre-PG BMI into LN and OB. We measured maternal plasma insulin, glucose, C-reactive protein (CRP), and DHA concentration (gas chromatography/mass spectrophotometry) and calculated the homeostatic model assessment for IR (HOMA-IR). As expected, IR was higher in OB women (Table 1). Maternal DHA was negatively correlated with maternal HOMA-IR (R²=0.25 p=0.001), and CRP (R²=0.15 p=0.004) among all women. These correlations persisted for OB women: HOMA-IR (R²=38 p=0.007), CRP (R²=0.20 p=0.01); but not for LN women. High maternal DHA is associated with lower inflammation and IR in OB PG women at term. We speculate that high pre-PG omega-3 intake has a significant metabolic impact on insulin sensitivity, especially in OB women.

Table 1.

<table>
<thead>
<tr>
<th>Lean (BMI: 16-24.9 kg/m²)</th>
<th>Obese (BMI&gt;30; n=26)</th>
<th>pValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational Age at delivery (wks)</td>
<td>38.6 ± 0.6</td>
<td>38.1 ± 0.4</td>
</tr>
<tr>
<td>Pre-Pregnancy BMI (kg/m²)</td>
<td>21.1 ± 2.2</td>
<td>38.1 ± 0.6</td>
</tr>
<tr>
<td>DHA (µM/L)</td>
<td>453 ± 197</td>
<td>347 ± 120</td>
</tr>
<tr>
<td>HOMA R</td>
<td>1.1 ± 0.8</td>
<td>2.4 ± 1.4</td>
</tr>
<tr>
<td>CRP (mg/mL)</td>
<td>5100 ± 2388</td>
<td>7859 ± 2138</td>
</tr>
<tr>
<td>Birth (Weight (g))</td>
<td>33 ± 0.4</td>
<td>35 ± 0.4</td>
</tr>
</tbody>
</table>

Supported By: Eunice Kennedy Shriver National Institute of Child Health and Human Development; Case Western Reserve University

Haptoglobin Concentration, Pregnancy, and Preeclampsia in Women with Type 1 Diabetes

CLARE B KELLY, JEREMY YU, ALICIA JENKINS, ALISON J NANKERVIS, KRIS-TIAN F HANSEN, SATISH K GARG, CHRISTOPHER A ASTON, TIMOTHY LYONS, Charleston, SC, Sydney, Australia, Parkville, Australia, Oslo, Norway, Aurora, CO, Oklahoma City, OK

Haptoglobin (Hp) binds the globin portion of free haemoglobin (Hb) thus inhibiting oxidative damage: it also has anti-inflammatory and pro-angiogenic properties. There are two Hp alleles and three phenotypes, Hp 1-1, Hp 1-2, and Hp 2-2, the latter is present in ~50% of people, and is associated with cardiovascular risk and declining renal function in diabetes patients. Preeclampsia (PE) occurs more frequently in diabetic than nondiabetic women (~29% vs. ~5%): reasons are not fully elucidated, but oxidative stress, inflammation, and altered angiogenesis are implicated.

We determined maternal plasma Hp levels (ELISA, R and D Systems) and Hp phenotype (ELISA, Savyon Diagnostics Ltd) in a prospective study of 23 pregnant women with type 1 diabetes (T1D) who developed PE, 24 who remained normotensive, and 19 pregnant normotensive nondiabetic women. Samples were collected at 3 visits (V1-V3) (12.4 ± 1.8, 21.7 ± 1.4, and 31.3 ± 1.4 weeks gestation (mean ± SD)). All subjects were free of microalbuminuria and hypertension at enrolment, and all visits preceded clinical PE onset.

Results: Longitudinal analyses revealed significant temporal decreases of plasma Hp during pregnancy in T1D women who developed PE (p=0.001) and in nondiabetic normotensive women (p=0.017), but not in T1D who remained normotensive. Among all T1D women, plasma Hp was lower in those with Hp 2-2 vs. non-Hp 2-2 phenotype at V2 (p=0.005) and V3 (p=0.002), independent of PE status. In Hp 2-2 T1D women only, plasma Hp was higher in those who did vs. did not develop PE at V1 (77.0 ± 31.4 vs. 50.7 ± 14.5 mg/dl) (p=0.033) and V2 (61.9 ± 19.0 vs. 42.0 ± 21.5) (p=0.046). Plasma Hp correlated positively with CRP at all visits (p<0.005), but not with previously-measured anti-angiogenic/angiogenic factors.

Conclusion: Maternal plasma Hp may serve as an early marker for PE in T1D pregnancy, particularly in women with the Hp 2-2 phenotype.

Longitudinal Changes in Amino Acid (AA) Turnover in Pregnancy in Women with Normal Glucose Tolerance (NGT) and GDM—Relationship to Fetal Growth

PATRICK CATALANO, LARRAINNE PRESLEY, SYLVIE HAUGUEL DE MOUZON, SATISH KALHAN, Cleveland, OH

GDM have decreased glucose insulin sensitivity vs. NGT. However, there are less data on the impact of GDM on AA metabolism or relationship to fetal growth. Ten NGT and 8 GDM (> 1 abnormal value, 3 hour OGTT) were evaluated at 18-22 and 32-36 weeks. For 2 potent amino acid secretagogues, Phenylalanine (PHE) and Leucine (LEU), PHE and LEU turnover was estimated (DS PHE and 13C LEU) under basal and euglycemic hyperinsulinemic clamp conditions. Neonatal body composition was estimated using anthropometrics. There were no significant difference in maternal age, race, education, tobacco use, weight or body composition between NGT and GDM at 18-22 weeks. The was a higher family hx of diabetes in GDM (p=0.05). Basal LEU but not PHE turnover increased over time and was greater in GDM. Table. Glucose disposal decreased over time and was lower in GDM. During the clamp LEU but not PHE turnover increased over time and was greater in GDM. Clamp PHE turnover (µmol/kg/hour) at 18-22 weeks correlated with neonatal lean mass (r=0.49, p=0.048) and there was a trend for fat mass (r=0.47, p=0.058). Omitting 1 outlier there remained a trend for PHE turn-over and neonatal lean mass (r=0.43, p=0.08). Leu turnover increased over time and was greater in GDM vs. NGT. In contrast, there were no significant changes in PHE turnover over time or between groups but PHE turnover in early pregnancy was related to fetal lean mass.

Table.

<table>
<thead>
<tr>
<th>Lean (BMI: 16-24.9 kg/m²)</th>
<th>Obese (BMI&gt;30)</th>
<th>pValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal Leucine turnover (µmol/kg<em>h)</em></td>
<td>12-16 weeks</td>
<td>129.9 ± 19.9</td>
</tr>
<tr>
<td>32-36 weeks</td>
<td>134.1 ± 22.0</td>
<td>157.0 ± 29.9</td>
</tr>
<tr>
<td>Leucine turnover (µmol/kg<em>h)</em></td>
<td>12-16 weeks</td>
<td>108.5 ± 18.5</td>
</tr>
<tr>
<td>32-36 weeks</td>
<td>123.0 ± 19.8</td>
<td>139.2 ± 21.8</td>
</tr>
</tbody>
</table>

Supported By: National Institutes of Health

Is Gestational Weight Gain Associated with Change in Ectopic Lipid Stores?

KIMBERLY VESCO, MICHAEL C. LEO, MELANIE FRANCISCO, ERIC BAETSCHER, WILLIAM ROODNEY, NICOLE E. MARSHALL, JONATHAN G. PURNELL, Portland, OR

Background: In nonpregnant adults, increased ectopic lipid stores [intrahepatic (IHL) intramyocellular (IMCL)] are associated with increased risk of diabetes mellitus and nonalcoholic fatty liver disease. While the amount of weight gained during pregnancy is significantly associated with the amount of weight retained after delivery, it is unclear whether weight gain during pregnancy is correlated with increased IHL or IMCL stores; thus, predisposing women with postpartum weight retention to increased risk of diabetes and NAFLD.

Methods: We evaluated 36 women with an enrollment BMI between 18.5 and 36 kg/m² at a mean (min-max) of 15.6 (12.9-17.3) weeks gestation and again at 34.2 (32.1-37.7) weeks gestation. Women with pregestational diabetes and multifetal pregnancies were excluded. Participants underwent 1h magnetic resonance spectroscopy to assess IHL and IMCL content, and air displacement plethysmography to assess body weight, percent (% body fat, fat mass, and lean mass.

Results: The participants were primarily white (89%) with mean age of 30.4 years. Table shows mean, standard deviation (SD), and Pearson's correlation coefficients for all measures. Conclusion: Gestational weight gain tracks closely with increase in fat mass during pregnancy, but is not significantly correlated with change in IHL or IMCL stores.
**Haptoglobin Phenotype Modulates Lipoprotein-Associated Risk for Preeclampsia in Women with Type 1 Diabetes**

CLARE B. KELLY, JEREMY YU, ALICIA J. JENKINS, ALISON J. NANKERVIS, KRISTIAN F. HANSEN, SATISH K. GARG, CHRISTOPHER E. ASTON, TIMOTHY LYONS, Charleston, SC, Sydney, Australia, Parkville, Australia, Oslo, Norway, Aurora, CO, Oklahoma City, OK

Preeclampsia (PE) occurs more frequently in pregnant diabetic than non-diabetic women (~20% vs. ~5%). Early identification of high risk women is needed. Dyslipidemia is implicated: we previously showed that early in pregnancy, increased cholesterol-rich lipoproteins are associated with subsequent PE in type 1 diabetes (T1D). Haptoglobin (Hp) is a plasma protein that binds free hemoglobin, and has two allelic forms, Hp-1, Hp-2, hence three phenotypes. Among people with diabetes, Hp 2-2 phenotype (present in ~40%) has been associated with oxidative stress, cardiovascular risk and renal decline.

We investigated whether maternal Hp phenotype is associated with PE in T1D, and/or modulates lipoprotein-related risks for PE. A prospective study of pregnancy included 23 T1DM women (cases) who developed PE, and 24 T1DM (controls) who remained normotensive. All were free of microalbuminuria and hypertension at enrolment. Hp phenotype was determined by ELISA (Savyon Diagnostics Ltd.). Lipid profiles were measured at three study visits (V1-V3), all preceding PE onset: (mean ± SD) 12.4 ± 1.8, 21.7 ± 1.4, and 31.3 ± 1.4 weeks gestation.

Results: Hp phenotype did not differ between women with and without PE, and lipid profiles did not differ by Hp phenotype. In PE cases vs. controls, by univariate analysis, HDL-C was lower at V1 (1.9±0.4 vs. 2.2±0.5 mmol/l (mean ± SD)), while LDL-C was higher at V2 (3.1±1.0 vs. 2.6±0.8 mmol/l), as were triacylglycerols (1.8±0.4 vs. 1.3±0.4 mmol/l) (p<0.05). In Hp 2-2 women, these associations were stronger: in 2-2 cases vs. 2-2 controls (n=9), HDL-C was lower at all visits (V1: p<0.05; V2, V3: p<0.01) and LDL-C was higher at V1 (p<0.01) and V2 (p<0.05). In contrast, in women with one or two Hp-1 alleles, no associations between lipids and PE were observed.

Conclusion: In T1D women, lipoprotein-related risks for PE may be limited to those with Hp 2-2 phenotype. The data provide further evidence of a role for Hp phenotype as a modulator of vascular risk in diabetes.

**Adipose Tissue Health Associates with the Development of Gestational Diabetes Mellitus in Nonobese Women**

DEMIDMAA R. TUVDENDORJ, BATBAYAR TUMURBAATAR, AARON POOLE, SHWETHA THUKUNTLA, GAYLE O. KOUTROVELIS, NICOLA ABATE, Galveston, TX, Portsmouth, VA, League City, TX

Background: Gestational diabetes mellitus (GDM) associates with health complications in both mother and child. Obesity and impaired adipose tissue (AT) health associate with the development of GDM. However, recent studies have shown that impaired AT health may occur in the absence of obesity.

In this study we studied if AT health associates with the development of GDM in non-obese women. Method: Pregnant women diagnosed with GDM were studied. Age- and body mass index (BMI)-matched non-GDM women were enrolled as Controls (n=6 per group). Fasting blood and AT samples were obtained before and during cesarian section, respectively. The serum levels of adiponectin were measured using Bioplex assay. The expression of phosphorylated p38 (p-p38) in AT was measured using Western blotting, and the average values of adipocyte sizes were estimated. The differences in variables between the groups were determined using two-tailed unequal variance Student t test; p < 0.05 was considered as statistically significant.

Results: There were no difference in age (Control vs. GDM: 31±1 vs. 32±1 years, p = 0.852). In the GDM group, the serum concentration of adiponectin was significantly lower (Control vs. GDM: 16±3 vs. 7±1, p = 0.021); while the AT expression of p-p38 was significantly higher (Control vs. GDM: 0.55±0.14 vs. 1.42±0.23, p = 0.013). The adipocyte size was 11% lower in the GDM group, although the difference did not reach statistical significance (Control vs. GDM: 100±8 vs. 89±5, p = 0.173).

Conclusion: Our data demonstrate that AT health may play a significant role in the development of GDM in non-obese women. Future studies to determine the mechanisms whereby AT health leads to the development of GDM in the absence of obesity are warranted.

**IRIS1 is a Target of MicroRNA-126**

JEANIE B. TRYGGESTAD, APRIL M. TEAGUE, STEVEN CHERNAUSEK, Oklahoma City, OK

Exposure to diabetes in utero has been shown to program offspring toward cardiometabolic disease and diabetes (DM). Alteration of fetal microRNA expression is a potential mechanism that mediates the effects of maternal conditions on the fetus. In previous work, we have shown that microRNA-126 expression is increased in umbilical vein endothelial cells (HUVEC) and in cord blood from infants born to mothers with DM. In this study we evaluated the capacity of microRNA-126 to target IRIS1 mRNA by binding to a complementary sequence in the 3’UTR. A commercially available plasmid (SwitchGear Genomics) containing the 3’UTR of IRIS1 with a lucifer-
IGFs and IGF-Binding Proteins in Pregnancy and Gestational Diabetes Mellitus

KATERÍNA ANDERLOVÁ, PATRÍK SIMJAK, ANNA CINKAJZLOVÁ, JAN KLOČUKOVA, HELENA KRATOCHVÍLOVÁ, ZDENA LACINOVÁ, PETRA KAVÁLKOVÁ, HANA KREJCÍ, MILOS MRÁŽ, MARTIN HALUZÍK, MIHÁL KRSEK, PAGUE, CZECH REPUBLIC

The insulin-like growth factor (IGF) axis is involved in the regulation of growth and metabolism; however, little is known about its role in the development of gestational diabetes mellitus (GDM). The aim of our study was to determine serum IGF-1, IGF-2 and selected IGF binding protein (IGFBP) levels and their mRNA expression in subcutaneous (SAT) and visceral adipose tissue (VAT) together with systemic levels and mRNA expression of selected inflammatory markers in these depots and placenta. Thirty-seven pregnant females - 21 with GDM (GDM group) and 16 without GDM (P group) - were included into the study. Blood samples were taken in 26th-32th and 36th-38th gestational week and 6-12 months after delivery and SAT, VAT and placental samples were obtained during delivery. Lymphocytes were assessed as percent of CD45+ cells measured by flow cytomtery. In both groups CD45+ lymphocytes were higher in VAT compared to SAT (19.2 ± 2.2 vs. 16.9 ± 0.7%, p=0.011 for GDM and 18.3 ± 3.4 vs.7.8 ±1.6, p=0.008 for P, respectively). In GDM group T helper (CD4+) cells were higher in SAT compared to VAT (37.6 ± 2.4 vs. 28.6 ± 2.6%, p=0.019), resulting in a higher ratio of CD4+/CD8+ cells. Similarly, the amount of B (CD19+) and NK (CD16/56+CD3+) cells was higher in SAT relative to VAT in GDM group, but not in P group. In contrast, NK (CD16/56+CD3+) cells were increased in VAT compared with SAT in GDM group (17.9 ± 3.1 vs. 9.1 ± 1.3%, p=0.015), while no difference was seen in P group. CRP levels did not differ between GDM and P group, while TNF-α concentrations were higher in GDM throughout the study (7.92 ± 0.69 vs. 4.39 ± 0.61 pg/ml, p=0.001). Placental mRNA expression of IL-10 and IL-8 was elevated in GDM vs. P group with no difference between SAT and VAT depots. Taken together GDM is associated with increased systemic TNF-α levels and changed lymphocyte content in different adipose tissue depots. These changes could be in part responsible for increased risk of complications for both mother and child during and after pregnancy.

Supported By: Ministry of Health of the Czech Republic (VFN64165, AVZ5-27630A)

Moderated Poster Discussion: Clinical/Epidemiology Topics in Gestational Diabetes Mellitus (Posters: 1414-P to 1419-P), see page 17.

Metformin and Dietary Advice for Pregnant Women Who Are Overweight or Obese to Promote Gestational Restriction of Weight—The GROW Randomized Trial

JODIE M. DODD, JENNIE LOUISE, ANDREA R. DEUSSEN, THE GROW RANDOMIZED TRIAL GROUP, NORTH ADELAIDE, AUSTRALIA

Background: Maternal obesity and gestational diabetes are characterised by insulin resistance, hyperglycemia, and low-grade chronic inflammation, contributing to excess availability of nutrients and fetal growth. Metformin is used increasingly in treatment of gestational diabetes.

Aim: To evaluate the effects of prenatal metformin among overweight and obese pregnant women on maternal and infant outcomes.

Methods: We conducted a randomized, placebo controlled trial. Women were recruited from public maternity hospitals in Adelaide, with a singleton, pregnancy between 10+0 and 20+6 weeks, and BMI ≥25.0 kg/m2 at their first antenatal visit. We used a computer randomization service, with stratification for parity, BMI (overweight vs. obese) and center of birth. Women were randomized to either metformin or Placebo. Women used metformin tablets (up to 2g daily) or identical appearing placebo. All women received a dietary and lifestyle intervention, consisting of three face-to-face sessions and three telephone calls over their pregnancy. Outcomes included infant birth weight >4kg, gestational weight gain, gestational diabetes and other pregnancy and birth outcomes.

Results: We randomized 524 pregnant women. Baseline characteristics at randomization were comparable. Women who received prenatal metformin in addition to the dietary intervention gained significantly less weight during pregnancy compared with women who received the dietary intervention and placebo (β7.7 ± 5.9kg vs. 8.9 ± 7.9kg, mean difference -1.16 (95% CI -2.3 to 0.02).

Supported By: National Institute of Diabetes and Digestive and Kidney Diseases

IGF-1 is decreased by miR-126-3p. A 1.5-fold reduction is seen in IGF1 exposed to miR-126-3p.

Supported By: National Institute of Diabetes and Digestive and Kidney Diseases

ADA-Supported Research

Moderated Poster Discussion
to -0.05; p=0.04). There were no statistically significant differences with regards other clinical outcomes, including diagnosis of gestational diabetes.

Conclusions: The combination of prenatal metformin and a dietary inter-
vention reduced gestational weight gain during pregnancy, but did not impact clinical pregnancy and birth outcomes.

Supported By: National Health and Medical Research Council of Australia (1043181)

The Association of Pregnancy Number and Outcome with Morbidity in Type 1 Diabetes TINA COSTORELLA, JESSICA RUBINSTEIN, TREVOR J. ORCHARD, Pittsburgh, PA

Women with type 1 diabetes are at greater risk of adverse pregnancy out-
comes and complications compared with the general population. Whether the number and outcome of pregnancies predict mortality risk, however, is not well studied. We thus assessed this hypothesis among women with childhood-onset type 1 diabetes. Female participants (n=325, mean age 29 and duration 19 years) of the Pittsburgh Epidemiology of Diabetes Complications (ECD) study, a prospective investigation of childhood onset type 1 diabetes, were selected for study. Pregnancy data were available for 320 women (98.5%). During 25 years of follow-up, 25.9% died (n=83). Exclud-
ing women (n=4) with twin pregnancies, no differences were observed in the proportion having been pregnant or in the number of pregnancies by mortality status. However, among those with at least one pregnancy (and adjusting for the total number of pregnancies), deceased were more likely to have had fewer live births and induced abortions but a greater number of spontaneous abortions and stillbirths (all p<0.05). In multivariable Cox model adjusting for traditional baseline risk factors, having ever been pregnant was associated with a borderline inverse mortality risk (HR=0.85, p=0.07). In addition, among women with at least one pregnancy, adjusting (among other risk factors) for the total number of pregnancies, ≥2 spontaneous abortions (HR=3.5, p=0.03; ≥2 stillbirths (HR=9.1, p=0.02); and ≥2 occurrences of any adverse pregnancy outcome (i.e., tubal/ectopic pregnancies, spontaneous abortions, stillbirths; HR=3.9, p=0.007) were associated with an increased risk of death. Women whose pregnancy outcomes were all spontaneous abortions were at a tenfold increased risk for mortality (p=0.004) whereas those with all preterm births were 76% less likely to die (HR=0.24, p=0.08).

In conclusion, adverse pregnancy outcomes among women with type 1 diabetes are associated with a greater mortality risk even after adjustment for traditional risk factors and diabetes control.

Supported By: National Institutes of Health (DK34818); Rossi Memorial Fund

A Reduction in Sedentary Behavior in Obese Women Reduces Neonatal Adiposity—The DALI Randomized Controlled Trial MIREILLE VAN POPPEL, DAVID SIMMONS, GERNOT DESOYE, DALI CORE INVESTIGATOR GROUP, Graz, Austria, Campbelltown, Australia

Background: Maternal obesity and gestational weight gain are implicated in the development of childhood obesity tracking from neonatal adiposity. Lifestyle intervention in pregnancy might reduce adverse effects of mater-
nal obesity on neonatal adiposity.

Methods: In the Vitamin D And Lifestyle Intervention (DALI) Lifestyle trial, 436 women with a body mass index ≥ 29 kg/m² were randomly assigned to counseling on Healthy Eating (HE), Physical Activity (PA), HE&PA, or to usual care (UC). Neonatal outcomes were head, abdominal, arm and leg circumfer-
ence, skin folds, estimated fat mass, fat percentage, fat free mass, and cord blood leptin. Reduced sedentary behavior seemed to drive the intervention effect on cord blood leptin. Implications for future adiposity of the offspring need to be elucidated.

Supported By: European Union Seventh Framework Program (242197)

Associations of a Preconception Biomarker Risk Score with Future Gestational Diabetes SYLVIA E. BADON, ASSIAMARA FERRARA, YEYI ZHU, SNEHA B. SRIDHAR, CATH-
ERINE LEE, SAMANTHA EHRLICH, CHARLES QUESENBERY, MONIQUE HEDDER-
SON, Oakland, CA, Knoxville, TN

Individual preconception biomarkers have been associated with future gestational diabetes mellitus (GDM) risk. Creating a biomarker risk score incorporating several biomarkers may enhance identification of women at high risk for GDM before pregnancy. The objective of this study was to develop a preconception biomarker risk score and assess its association with subsequent GDM. We conducted a nested case-control study within a cohort of 4,036 women with serum and questionnaire data collected as part of a health checkup (1984-1996) and a subsequent pregnancy (1984-2009) in northern California. Two controls were matched to each GDM case (N=256 cases) on year and age at serum collection, age at pregnancy, and number of pregnancies between serum collection and index pregnancy. Biomarkers associated with GDM in univariable models were dichotomized into high/ low risk using quartiles. A biomarker risk score was created by summing the number of high risk biomarkers that were significantly associated with GDM in a multivariable model. Receiver-operating-characteristic curve analyses were used to assess the incremental predictive value of the biomarker risk score beyond conventional GDM risk factors obtained from medical records (age, race/ethnicity, BMI, family history, previous GDM). Compared to low risk, high risk levels of total adiponectin (≥72 μg/ml), SHBG (≥4.2 nmol/L), and HOMA-IR (≥3.9) were each independently associated with 2.03 (95% CI: 1.37, 3.02), 2.78 (95% CI: 1.87, 4.13), and 2.07 (95% CI: 1.40, 3.06) times the odds of GDM and thus included in the biomarker risk score. For each one unit increase in the biomarker risk score, odds of GDM were 2.04 times greater (95% CI: 1.62, 2.58). The biomarker risk score had relative incremen-
tal predictive value beyond conventional GDM risk factors (AUC= 0.73 vs. 0.67, P<0.0001). Our results suggest the biomarker risk score has potential clinical utility in preconception risk assessment for GDM beyond conven-
tional clinical risk factors.

Supported By: Eunice Kennedy Shriver National Institute of Child Health and Human Development (R01HD065904)

Comparison of Cardiometabolic Risk Factors in Offspring of Diabetic Mothers (GDM) and Non-diabetic Mothers (OND) in India SONALI S. WAGLE, KALYANARAMAN KUMARAN, RASHIKA LADKAT, DATTATRAY BHAT, PALLAVI C. YAJNICK, CHITTARANJAN S. YAJNICK, Pune, India, Southampton, United Kingdom

Background: Maternal diabetes is a risk factor for obesity and glucose intolerance in the child, and contributes to the escalating epidemic of dia-
betesy. This sparse data is available in India. We followed children born to diabetic and non-diabetic mothers 2-26 years after delivery to assess their cardiometabo-
litic risk factors.

Methods: 01661 women diagnosed and treated for diabetes in pregnancy (1988-2016), we tracked 246 and studied 200 children (ODM). We also studied 177 children of non-diabetic mothers (OND), matched for age, gender and socioeconomic status. We measured anthropometry, body composition (DXA) and a capillary blood glucose (<10y, 119 ODM, 93 OND) or a 1.75g/ kg OGTT with venous blood (>10y, 81 ODM, 84 OND). Overweight-obesity was diagnosed by IOTF (>18y) or WHO criteria (>18y). Glucose tolerance was classified by the ADA 2014 criteria. We compared cardio-metabolic risk fac-
tors in ODM and OND by calculating age and gender specific SD scores (reference OND).

Results: Three (4%) ODM were known diabetic (diagnosed at 16, 14 and 23y, 2 receiving OHA and 1 insulin), one was diagnosed on testing. ODM had higher BMI, skinfolds, body fat percent, and circulating glucose, insulin, total and LDL cholesterol, and triglyceride concentrations. ODM had higher HOMA-IR and pulse rate but lower disposition index (HOMA-IR/pulse rate) and diastolic blood pressure. Prediabetes (IFG+IGT) (37 vs. 20%, p=0.005) and overweight-obesity (24 vs. 15%, p=0.014) were more common in ODM compared to OND.

Conclusions: We confirm elevated risk of obesity, adiposity, diabetes and other cardio-metabolic risk factors in children of Indian diabetic mothers. Despite following the current standards of practice for GDM management, the offspring continue to have high risk of diabetes. This suggests a need for reevaluation of current standards of care which overlook the peri-conceptional window of fetal programming.

Supported By: Government of India Department of Biotechnology

Clinical Diabetes/Therapeutics POSTERS

PREGNANCY—CLINICAL/EPIDEMIOLOGY

1415-P

A Reduction in Sedentary Behavior in Obese Women Reduces Neonatal Adiposity—The DALI Randomized Controlled Trial

MIREILLE VAN POPPEL, DAVID SIMMONS, GERNOT DESOYE, DALI CORE INVESTIGATOR GROUP, Graz, Austria, Campbelltown, Australia

Background: Maternal obesity and gestational weight gain are implicated in the development of childhood obesity tracking from neonatal adiposity. Lifestyle intervention in pregnancy might reduce adverse effects of maternal obesity on neonatal adiposity.

Methods: In the Vitamin D And Lifestyle Intervention (DALI) Lifestyle trial, 436 women with a body mass index ≥ 29 kg/m² were randomly assigned to counseling on Healthy Eating (HE), Physical Activity (PA), HE&PA, or to usual care (UC). Neonatal outcomes were head, abdominal, arm and leg circumference, skin folds, estimated fat mass, fat percentage, fat free mass, and cord blood leptin. Intervention effects on neonatal outcomes were assessed in multilevel analyses. Mediation of intervention effects by lifestyle and gestational weight gain was assessed.

Results: Outcomes were available from 324 neonates. A reduction in sum of skin folds (≤1.8 mm, 95% CI, -3.5 to -0.2, p=0.03), fat mass (≤63 g, 95% CI, -124 to -2, p=0.04), fat percentage (≤1.2%, 95% CI, -2.4 to 0.4, p=0.04), and cord blood leptin (≤3.80 μg/l; 95% CI, -9.43 to -0.14, p=0.05) compared to UC. Reduced sedentary behavior seemed to drive the intervention effect on cord blood leptin. Implications for future adiposity of the offspring need to be elucidated.

Supported By: European Union Seventh Framework Program (242197)
The Association between Free Fatty Acid Level at Midpregnancy and Postpartum Glucose Intolerance in Women with Gestational Diabetes Mellitus

KYUNG-BOI KIM, SOO-KYUNG KIM, YOUNG-WOOK CHO, SEOK WON PARK, Seongnam, Republic of Korea

Free fatty acid (FFA) is correlated with fetal growth during pregnancy and with neonatal fat mass in women with gestational diabetes mellitus (GDM). However, there are few studies between FFA level and postpartum glucose metabolism in women with GDM. The aim of this study was to evaluate the association between FFA level at mid-pregnancy and postpartum glucose intolerance in women with GDM. We enrolled 769 pregnant women diagnosed with GDM from February 2009 to October 2016. FFA levels (fasting and postprandial 2-h) were measured during 24-32 gestational weeks and 75-g OGTT was performed at 6-12 weeks after delivery. High FFA was defined by more than the median level of FFA at mid-pregnancy. Postpartum glucose intolerance was defined as fasting plasma glucose (FPG) ≥ 100 mg/dL or 2-h plasma glucose (2-h PG) ≥ 140 mg/dL. Mean age was 33.1 years and mean pre-pregnancy BMI was 22.4 kg/m². The prevalence of postpartum glucose intolerance was 48.0% (n = 369). Although postprandial 2-h FFA level and FFA difference (between fasting and postprandial 2-h FFA) were not significantly different between two groups, women with postpartum glucose intolerance had higher fasting FFA level at mid-pregnancy than those with normal glucose tolerance (733.7 μg/L vs. 700.6 μg/L, P < 0.049). Compared to women with low fasting FFA, women with high fasting FFA had higher postpartum glucose intolerance (51.8% vs. 44.1%, P = 0.033). After adjustment for maternal age, pre-pregnancy BMI, parity, family history of diabetes, FPG, and lipid measures (total cholesterol, triglyceride, HDL-cholesterol), women with high fasting FFA were 1.47 times (95% CI 1.07-2.01) more likely to have postpartum glucose intolerance than those with low fasting FFA. In women with GDM, high fasting FFA level at mid-pregnancy is associated with elevated risk of postpartum glucose intolerance.
Breastfeeding at Night Is Rarely Followed by Hypoglycemia in Puerperal Women with Type 1 Diabetes Using Carbohydrate Counting and Modern Insulin Treatment

LENE RINGHOLM, ANN B. ROSKJÆR, SUSANNE ENGBERG, HENRIK U. ANDERSEN, EVA HOMMELEN, ANNA L. SECHER, PETER DAMM, ELISABETH R. MATHIESEN, Gentofte, Denmark, Copenhagen, Denmark

Aim: Hypoglycemia in association with breastfeeding is a feared condition in women with type 1 diabetes. Thus, routine carbohydrate intake at each night-time breastfeeding is often recommended despite lack of evidence. We evaluated glucose levels during breastfeeding with focus on whether night-time breastfeeding induced hypoglycemia in women with type 1 diabetes.

Methods: Prospective study of 25 consecutive breastfeeding women (mean age 30.8 (SD ±5.9) years, 64% nulliparous, singleton pregnancy) with type 1 diabetes for 18.8 (±10.5) years. All were experienced in carbohydrate counting with 44% on insulin pump and 56% on multiple daily injections. At 33 (±7.2) and 66 (±14.2) days postpartum blinded continuous glucose monitoring (CGM) was applied for six days and the women recorded breastfeedings and carbohydrate intake.

Results: At both CGM periods mean glucose levels were similar at night (11 pm to 7 am) (8.3 (±1.7) and 8.7 (±2.1) mmol/l, p=0.56) and over 24 hours (8.4 (±1.5) and 8.7 (±2.1) mmol/l, p=0.56). The percentage of time <4.0 mmol/l was similar at night (median 5.8% (range 0-20.8) and 3.1% (0-36.1), p=0.24) and over 24 hours (5.0% (0-19.8) and 3.9% (0-22.8), p=0.75). At 33 days postpartum maternal weight was close to the pre-pregnancy weight (79.1 (±15.0) vs. 75.6 (±14.2) kg, p=0.50) while insulin dose was 18% lower than before pregnancy (p=0.04). A total of 340 night-time breastfeedings were recorded with 2 (0-4) breastfeedings per night. Carbohydrate was ingested at 42 (12%) of the breastfeedings. CGM <4.0 mmol/l within three hours after night-time breastfeeding occurred after 5% of breastfeedings.

Conclusion: Despite almost 300 night-time breastfeedings without carbohydrate intake, hypoglycemia within 3 hours after breastfeeding was rare. The recommendation of routine carbohydrate intake at night-time breastfeeding in women with type 1 diabetes on modern insulin treatment who count carbohydrate may be obsolete.
Clinical and Translational Sciences Institute
Women’s Health Research; University of Colorado College of Nursing; Colorado
obesity, and may contribute to higher patterns of glycemia. SDB may be
(r=0.55, p=0.02). ODI was correlated with both 24 hour AUC (r=0.54, p=0.02,
and 5.2±1.3, respectively. Importantly, AHI was correlated with 24 hour glu-
OSA). Total sleep time was 370.3±12.4 min (~6 hours), sleep efficiency was
desaturations
out gestational diabetes. At 33±1 weeks, 18 pregnant women without OSA
bolic function. We hypothesized that worse SDB in part accounts for higher
(SDB) and sleep apnea (OSA), is poorly understood in pregnancy, yet may insidiously worsen meta-
Aurora
Sleep Disordered Breathing—An Unrecognized Contributor to
1428‑P
Lab Induction and Cesarean Delivery Risk in Women with Gestational Diabetes Mellitus
MAUREEN S. HAMEL, MARTHA B. KOLE, DWIGHT ROUSE, ERIKA WERNER, Providence, RI
Objective: Previous studies suggest that labor induction is associated with an increased risk of cesarean delivery (CD), but more modern studies question this finding. In particular, it is uncertain how induction affects CD risk among women with gestational diabetes mellitus (GDM), who are often induced. Therefore, we sought to assess the risk of CD among women with GDM who presented for induction compared to those who presented in spontaneous labor.
Methods: Secondary analysis of a prospective cohort study of singleton pregnancies complicated by GDM. Women planning an elective or repeat cesarean were excluded. All women were delivered at a single institution. The primary outcome for this analysis was mode of delivery (CD vs. vaginal delivery). Women who presented for an induction were compared to those who presented in spontaneous labor (including rupture of membranes at 34 weeks or greater). Covariates, including gestational age at delivery were investigated as confounders and adjusted for if the p<0.05. The study had 80% power to detect an 18% decrease in the absolute rate of vaginal deliveries in the induction group compared to the spontaneous labor group with an alpha of 0.05.
Results: Of the 222 women meeting study inclusion criteria, 80 (36%) presented in spontaneous labor and 142 (64%) underwent induction labor. The overall CD rate was 21.6% (n=48). When comparing labor induction to spontaneous labor to, there was no significant difference in the CD rate (21.8% vs. 21.3% p=0.41). Women who were induced compared to those who labored spontaneously differed only with regard to BMI at delivery (p=0.04), and hypertension (p<0.01). Even after adjusting for these covariates, the risk of CD did not differ between groups (aOR 1.01 95% CI 0.51, 2.02). Moreover, the risk remained non-significant even when gestational age at the model. Conclusion: Induction of labor among women with GDM is not associated with an increased risk of CD and should not be avoided in an attempt to minimize CD risk.
Supported By: American Diabetes Association (1-16-ICTS-118 to E.W.)

Sleep Disordered Breathing—An Unrecognized Contributor to Abnormal Glycemic Profiles in Pregnancy
SARAH S. FARABIL, LINDA A. BARBOUR, TERI L. HERNANDEZ, Aurora, CO
Sleep disordered breathing (SDB), particularly obstructive sleep apnea (OSA), is poorly understood in pregnancy, yet may insidiously worsen metabolic function. We hypothesized that worse SDB in part accounts for higher 24 hour patterns of glycemia in late pregnancy complicated by obesity without gestational diabetes. At 33±1 weeks, 18 pregnant women without OSA symptoms (29±4.2 years [mean±SEM], BMI 34.3±6.0 kg/m²) were provided a eucaloric diet (50% carb, 35% fat) for 72 hour while wearing a continuous glucose monitor (CGM). SDB severity was measured in-home with a WatchPAT200 wrist-worn device and quantified by the apnea hypopnea index (AHI), apnea hypopneas/hour and oxygen desaturation index (ODI; O₂ desaturations ≥4%/hour). Surprisingly, 12/18 women had an AHI≥5 (mild OSA). Total sleep time was 370.3±12.4 min (~6 hours), sleep efficiency was impressively low (82±1.5%), and AHI and ODI were at least mild at 11.6±2 and 5.2±1.3, respectively. Importantly, AHI was correlated with 24 hour glu-
cose area-under-the-curve (AUC) (r=0.50, p=0.03) and mean 24 hour glucose (r=0.55, p=0.02). ODI was correlated with both 24 hour AUC (r=0.54, p=0.02, Figure 1a) and mean 24 hour glucose (r=0.58, p=0.01, Figure 1b). Poor sleep and undiagnosed mild OSA are common in late pregnancy complicated by obesity, and may contribute to higher patterns of glycemia. SDB may be a treatable risk factor potentially improving maternal and fetal outcomes.

1428‑P
1429‑P
Maternal Metabolites during Pregnancy Are Associated with Newborn Outcomes
RACHEL KADIAK, MICHAEL NOZDENSKII, OCTAVIOUS TALBOT, ALAN KUANG, JAMES R. BAIN, MICHAEL MUEHLBAUER, OLGA ELKAYEVA, SARA K. O’NEAL, LYNN P. LOWE, BOYD E. METZGER, DENISE SCHOLTENS, WILLIAM LOWE, JR., HAPI STUDY COOPERATIVE RESEARCH GROUP, Chicago, IL; Durham, NC
The maternal metabolome serves as a proxy for the fetus’s metabolic environment, but its impact on newborn outcomes is largely unknown. To address this, we determined the association of maternal metabolites with newborn adiposity and hyperinsulinemia in a multiethnic cohort of mother-newborn dyads. Targeted and nontargeted metabolomics assays were performed on fasting and 1 hour serum samples from 1600 mothers in four ancestry groups (Northern European, Afro-Caribbean, Mexican-American, and Thai) who participated in the Hyperglycemia and Adverse Pregnancy Outcome Study, underwent an OGTT at ~26 weeks gestation, and whose newborns had anthropometric measurements at birth. Maternal metabolite-newborn phenotype associations were investigated using 1) per-metabolite analyses within and across ancestries and 2) network analyses to identify interconnected metabolites associated with phenotypes. Meta-analyses demonstrated more associations of maternal 1 hour vs. fasting metabolites with newborn outcomes. At fasting, maternal triglycerides, valine, pyruvate, and acylcarnitine (AC) C20 were associated with newborn birthweight, cord C-peptide, and/or sum of skinfolds (SSF). At 1 hour, several amino acids (AAs), ACs, fatty acids (FA), and lipid metabolites were associated with one or more of these same outcomes in models adjusted for maternal BMI or glucose. For example, the branched-chain amino acid valine and its carnitine ester AC C4/6 were associated with cord C-peptide at 1 hour independent of maternal BMI or glucose. Network analyses revealed clusters of fast-
ing ACs, AAs, FA and lipid metabolites associated with cord C-peptide and SSF, with the addition of branched-chain and aromatic amino acids at 1 hour. Maternal metabolites during pregnancy, particularly 1 hour post glucose, are associated with fetal adiposity and hyperinsulinemia, independent of mater-
Supported By: National Institute of Diabetes and Digestive and Kidney Diseases (R01DK095963), Eunice Kennedy Shriver National Institute of Child Health and Human Development (R01HD34242, R01HD34243)

Maternal Central Obesity and Birth Size—A Mendelian Randomization Analysis
TAO HUANG, TINGTING GENG, Beijing, China, Singapore, Singapore
Background: Observational studies have illustrated that maternal central obesity is associated with birth size, including of birth weight, birth length and head circumference, but the causal nature of these associations remains unclear.
Objective: To test the causal effect of maternal central obesity on birth size and pubertal height growth using a Mendelian randomization (MR) analysis.
Methods: We performed two-sample MR using summary-level genome-wide public data from the Genetic Investigation of Anthropometric Traits (GIANT) Consortium and the Early Growth Genetics Consortium (EGG). Thirty-five single nucleotide polymorphisms (SNPs), 25 SNPs and 41 SNPs were selected as instrumental variables for waist-to-hip ratio adjust BMI (WHrAdjBMI), waist circumference adjust BMI (WCAdjBMI) and hip circum-
ference adjust BMI (HIPAdjBMI), respectively to test the causal effects of maternal central obesity on birth size and pubertal height using an inverse-variance-weighted approach.
Results: In this MR analysis, we found no evidence between genetic instru-
mental variables for waist circumference (WC) or waist-to-hip ratio (WHr) and the outcomes. We observed one standard deviation (SD) increase in hip circumference (HC) was associated with a 0.392 SD increase in birth weight (p=1.1×10⁻⁶) and a 0.168 SD increase in birth weight (p=7.1×10⁻⁵), respectively. In addition, higher genetically predicted maternal HP was strongly associ-
ated with the puberty heights (0.835 SD, p=8.4×10⁻¹⁰). However, HP was not associated with head circumference (p=0.172).
Conclusion: A genetic predisposition to higher maternal HP was causally associated with larger offspring birth weight, higher birth length, and pubertal height independent of maternal BMI. This study did not find evidence of a causal association between maternal WC, WHr and birth size.

Supported By: University of Colorado Anschutz Medical Campus Center for Women’s Health Research; University of Colorado College of Nursing; Colorado Clinical and Translational Sciences Institute

ADA-Supported Research  Moderated Poster Discussion
In Early Pregnancy, a High Proportion of Women with Type 2 Diabetes Have Lower Daily Carbohydrate Consumption than Recommended by the Institute of Medicine

BJÖRG ASBJÖRNSDÓTTIR, HELLE RUNNEBY, MARIANNE VESTGAARD, LENE RINGHOLM, DOTTE M. JENSEN, ANNE RABEN, PETER DAMM, ELISABETH R. MATHIESEN, Copenhagen, Denmark, Gentofte, Denmark, Odense, Denmark, Frederiksberg, Denmark

Aim: Maternal glucose is the primary metabolic substrate for fetal growth and a diet low in carbohydrates is common among young women in the Western world. To secure sufficient carbohydrate consumption in pregnancy, the Institute of Medicine (IOM) recommends a minimum daily consumption of 175 grams of carbohydrates, corresponding to approximately 150 grams from the major carbohydrate sources. We aimed to explore the carbohydrate consumption in early pregnancy among women with type 2 diabetes and, for comparison, in women with type 1 diabetes.

Methods: As part of routine care, all pregnant women with type 2 and type 1 diabetes have since 2013 been asked to hand in a 3-day dietary record focusing on carbohydrates at their first antenatal visit. In the present study, total daily self-reported carbohydrate consumption from major carbohydrate sources, presence of ketonuria, HbA1c, weight and daily physical activity were evaluated.

Results: Dietary records were available from 96 women with type 2 diabetes vs. 108 women with type 1 diabetes at median 71 (range 60-87) vs. 63 (56-76) gestational days (p=0.003) where HbA1c was 6.6±1.2% (49±13 mmol/mol) vs. 8.0±1% (48±13 mmol/mol) (p=0.08), respectively. Body weight was 90.8 (±22) vs. 75.5 (±15) kg (p=0.001), but average daily carbohydrate consumption was similar in the two groups (159±56 vs. 167±46 g, P=0.3), as was the level of physical activity (246±104 vs. 233±96 metabolic equivalent of task [MET]-hour/week, P=0.9). A high proportion of the women consumed fewer carbohydrates than recommended by the IOM (52% vs. 40%, P=0.08).

There was a low prevalence of ketonuria (>4 mmol/L, equivalent to blood ketones of approx. 0.2 mmol/L) (2% vs. 1%, P=0.6).

Conclusion: In conclusion, women with type 2 diabetes had similar carbohydrate consumption to women with type 1 diabetes, despite higher body weight. Lower carbohydrate consumption than recommended by the IOM was prevalent, and ketonuria was rare.

Adaptability of Closed-Loop during Labor, Delivery, and Postpartum—A Secondary Analysis of Data from Two Randomized Cross-over Trials in Type 1 Diabetes Pregnancy

JENNIFER M. YAMAMOTO, ZOE A. STEWART, MALGORZATA E. WILINSKA, SARA HARTNELL, ROMAN HOVORKA, HELEN R. MURPHY, Peter Damm, Elisabeth R. Mathiesen, Copenhagen, Denmark, Gentofte, Denmark, Odense, Denmark, Copenhagen, Denmark, Gentofte, Denmark, Odense, Denmark, Fredensborg, Denmark

This is an observational study of women who chose to continue closed-loop during labor, delivery and 48-hour postpartum period. Of the 32 women from two randomized crossover trials examining closed-loop in pregnancy, 27 (84.4%) continued closed-loop during this time. Women maintained glucose control in women with type 1 diabetes during labor, delivery and the 48-hour postpartum period. Of the 32 women, 27 (84.4%) continued closed-loop during this time. Women who used closed-loop during labor and delivery spent 82.0% (IQR 49.3, 93.0) of time in the target range, with a mean glucose level of 124±25.4 mg/dl. Closed-loop performed well throughout all modes of delivery (Table 1). In the 48-hour postpartum period, the mean glucose was 130±25.0 mg/dl. During this time women spent 83.3% (IQR 75.2, 94.6) time-in-target range. There was no difference in mean glucose in mothers of infants with neonatal hypoglycemia vs. those without (mean maternal glucose of 124±28.8 and 122±21.8 mg/dl, respectively; p=0.94). This study demonstrates that closed-loop insulin delivery is safe and effective in labor, delivery and the immediate postpartum period. Future research is needed to compare the biomedical efficacy of closed-loop with intensive insulin therapy and intra-partum sliding scale approaches.

Table 1. Glucose Control during Labor and Delivery by Mode of Delivery.

<table>
<thead>
<tr>
<th>Mode of Delivery</th>
<th>n=4</th>
<th>n=12</th>
<th>n=11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean glucose (mg/dl)</td>
<td>113±2</td>
<td>126±1</td>
<td>126±2</td>
</tr>
<tr>
<td>Median time-in-target %</td>
<td>83 (47, 88)</td>
<td>84 (48, 95)</td>
<td>78 (48, 93)</td>
</tr>
<tr>
<td>Median time below target %</td>
<td>0 (0, 3)</td>
<td>0 (0, 3)</td>
<td>0 (0, 2)</td>
</tr>
<tr>
<td>Median time above target %</td>
<td>15 (11, 22)</td>
<td>11 (6, 20)</td>
<td>15 (13, 51)</td>
</tr>
<tr>
<td>Median number of hypoglycemic events</td>
<td>0 (0, 1)</td>
<td>0 (0, 1)</td>
<td>0 (0, 1)</td>
</tr>
<tr>
<td>Number of women with a hypoglycemic event</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Supported by: National Institute for Health Research (HRM CDR-2013-08-0250), Gates Cambridge Trust Allen-Carey Scholarship in Women’s Health
of existing prospective evidence. Odds ratios (OR) for GDM by SHBG quartiles were estimated using conditional logistic regression.

Results: SHBG at GW 10-14 was significantly and inversely related to fasting glucose, fasting insulin, insulin resistance and HbA1c levels, and positively related to high-density lipoprotein and cholesterol levels at GW 15-26. Cases had lower SHBG levels compared to controls at GW 10-14 (median ± SD: 204.0 ± 97.6 vs. 220.9 ± 102.5 nmol/L) and 15-26 (205.6 ± 124.3 vs. 322.7 ± 105.1 nmol/L), yet the differences were not significant. Meta-analysis of 11 prospective studies, including ours, estimated SHBG levels to be 0.50 SD (95% CI: 0.36-0.65) lower among women with than without GDM.

Conclusions: Higher SHBG levels in early pregnancy was associated with a favorable glucose metabolic profile among pregnant women. Synthesis of prospective studies supports an inverse association between SHBG levels and GDM risk.

Supported By: Lilly France SAS; Roche Diagnostics France SA

PREGNANCY—CLINICAL/EPIDEMIOLOGY

Is Screening for Early Gestational Diabetes Mellitus Associated with a Better Prognosis? An Observational Study Including 8,713 Women

EMMANUEL COSSON, DORIAN SANDBERG, FRANÇOISE GARY, ISABELLE PHARISIEN, JEAN-JACQUES PORTAL, PAUL VALENCI, LIONEL CARBILLON, Bondy, France, Paris, France

In addition to screening for gestational diabetes mellitus (GDM) after 24 gestational weeks (GW), the IADPSG proposed to screen in early pregnancy and to refer women with early GDM (eGDM) for immediate care. The usefulness of this strategy is still unknown. We included women with a singleton pregnancy, without personal history of diabetes or bariatric surgery, who delivered in our hospital between 2012 and 2016. We compared the incidence of preeclampsia or large for gestational age infant or shoulder dystocia in women with an early screening before 22 GW -leading to care for eGDM (25(OH)D<92 nmol/L) or diabetes in pregnancy (HbA1c>5.9%) if present- (screened group) or without (unscreened group). Compared with women in the unscreened group (n=4,534, 53.3%), those in the screened group (n=4,079) had different ethnicities (p<0.0001) and more risk factors (14.0 vs. 14.9%, p=0.035 for GDM: overweight (48.6 vs. 45.7, p<0.01), personal history of GDM (6.4 vs. 4.3%, p<0.01) and macular edema (3.6 vs. 2.7%, p<0.05). Early screening increased from year 2012 to 2016 (p<0.001). In the early screened group, the prevalence of GDM and DIP was 22.6% (including 10.3% of eGDM) and 0.9%, respectively. In the unscreened group, the prevalence of GDM was 17.2% and DIP 1.2%. The rate of insulin therapy was 8.6% in the screened group and 5.6% in the unscreened group (p<0.001). The rate of the composite criterion was similar in the screened and unscreened groups (12.5 vs. 11.8%, p=0.3534), also when we only considered women with risk factors for GDM (14.0 vs. 14.9%, p=0.01317). The incidence of other outcomes was similar in both groups. To conclude, a strategy including early FPG measurement during pregnancy may not improve pregnancy prognosis but we still need to adjust for the results for confounding factors (ongoing) because the women in the early-screened group had a similar prognosis as those only screened after 22 GW despite a higher risk of complications.

Supported By: Lilly France SAS; Roche Diagnostics France SA

Vitamin D Status during Pregnancy and the Risk of Gestational Diabetes Mellitus—A Longitudinal Study in a Multiracial Cohort

JIN XIA, YIDING SONG, SHRISTI RAVAL, JING WU, STEFANIE HINKLE, MICHAEL Y. TSIAI, CUIJIN ZHANG, Indianapolis, IN, Newark, NJ, Bethesda, MD, Minneapolis, MN

Background: Emerging evidence suggests that vitamin D status in pregnancy may be associated with the development of gestational diabetes (GDM). However, the temporal relationship remains unclear due to the lack of prospective data with serial measurements of maternal vitamin D levels. We prospectively examined longitudinal changes in vitamin D biomarkers in relation to subsequent GDM risk.

Methods: A nested case-control study of 107 GDM cases and 214 controls (matched on age, race/ethnicity, and gestational week (GW) at blood draw) was conducted within the NICHD Fetal Growth Studies-Singleton Cohort (2009-2013). Plasma concentrations of D2 and D3 25-hydroxyvitamin D (25(OH)D) and vitamin D binding protein were measured at GWs 10-14, 15-26, 23-31, and 33-39; we further calculated total, free, and bioavailable 25(OH)D. Linear mixed-effects models and conditional logistic regression models were used adjusting for confounders.

Results: Compared with controls, women who developed GDM appeared to have lower concentrations of total 25(OH)D as early as GWs 10-14 (median: 25.59 vs. 27.46 ng/mL) and had a greater longitudinal increase in total 25(OH)D levels from GWs 10-14 to 15-26 (LS mean difference in log-scale: 0.10 vs. 0.04, p=0.046). We found no linear associations between vitamin D biomarkers at GWs 10-14 or GWs 15-26 and GDM risk. However, vitamin D deficiency (<20 ng/mL) at GWs 10-14 was associated with a 2.82-fold increased GDM risk (adjusted OR=2.82, 95% CI: 1.15-6.93). Furthermore, women with persistent vitamin D deficiency at both weeks 10-14 and weeks 15-26 had more than 4-fold elevated risk for GDM compared to those persistently non-deficient (adjusted OR=4.46, 95% CI: 1.15-17.3).

Conclusions: Our findings suggest that maternal vitamin D deficiency in the first trimester of pregnancy may be implicated in the development of GDM. Assessment of vitamin D status in early pregnancy may be clinically important and valuable for the primary prevention of GDM.

Supported By: Eunice Kennedy Shriver National Institute of Child Health and Human Development (HHSN275201000013C, HHSN275200800002C, HHSN2750200800003C, HHSN2750200800014C, HHSN275200800012C, HHSN27520000009C, HHSN275200000100D)

How Important Is Early Diagnosis and Intense Insulin Therapy in In Vitro Fertilization Pregnancies Complicated by Gestational Diabetes Mellitus?

PETROS THOMAKOS, OLGA KEPATSOGLOU, ANASTASIA TROUVA, CAROL BARETTO, DIMITRIS TROUVAS, IBRAHIM TARAOUNE, ASTERIS KORANTZIS, CHRISTOS ZOUPAS, Athens, Greece

GDM is increased in IVF pregnancies. There is limited literature on GDM screening and management of IVF pregnancies. The aim was to investigate the impact of GDM management on the outcome of IVF pregnancies. The study was conducted with 102 singleton IVF (a), 102 GDM spontaneous conceptions (b) vs. 102 normal pregnancies (c). The group characteristics: [age: 38.2±4 vs. 34.1±3 vs. 37.4±4 years, p<0.001 (a vs. b), NS (a vs. c), <0.001 (b vs. c)]; BMI: 25.8±5 vs. 23.4±3 vs. 27.4±4 kg/m², p<0.001 (a vs. b), <0.001 (a vs. c), NS (b vs. c); HbA1c: 5.2±0.5 vs. 5.2±0.7 vs. 7.0±1.3%, p=NS (a vs. b), <0.001 (a vs. c), <0.001 (b vs. c); FBG: 84±1.8 vs. 84±2.7 vs. 78±2.5 mg/dl, p=NS (a vs. b), <0.001 (a vs. c), <0.001 (b vs. c); 1-hour postprandial blood glucose, fasting insulin, insulin resistance and HbA1c levels, and positively related to high-density lipoprotein and cholesterol levels at GW 15-26.

Weeks at delivery: 36.9±2 vs. 37.4±0.7 vs. 38±1.8, p=0.04 (a vs. b), p=0.001 (a vs. c), p=0.001 (b vs. c); neonatal birth wt. (in grams): 2891±341 vs. 3117±347, p=NS (a vs. b), <0.001 (a vs. c), p=0.001 (b vs. c); preeclampsia rate: 4.9 vs. 3.9 vs. 1.9%, Respiratory Distress Syndrome: 14.7 vs. 12 vs. 5.8%; Neonatal hypoglycemia: 17.6 vs. 14.7 vs. 3.9%, NICU admits: 14.7 vs. 15.6 vs. 5.8%, C-Section: 86.3 vs. 56.9 vs. 41.1%. Associations between characteristics and adverse outcomes were tested among the IVF group. 1-hour Postprandial BG, but not FBG nor HbA1c, was associated with maternal-fetal complications (n=504, p<0.001). Maternal hypoglycemia did not affect fetal outcome. Age and BMI were not correlated with the week of GDM diagnosis. The data emphasizes the importance of strict postprandial metabolic control reached by intense early insulin therapy limiting the incidence of adverse pregnancy outcomes. IVF pregnancies must be screened for GDM much earlier than 24-28 weeks.
 insulin secretory response between EP and PP using simple linear regression.
Results: Participants had a mean (standard deviation) age of 32.3 (5.0) years and BMI of 24.9 (4.9); 43% were nulliparous and 43% were racial/ethnic minorities. In EP vs. PP, insulin secretory response (Stumvoll 1st phase estimate) was 1474 (706) vs. 1221 (398) pmol/L, while insulin sensitivity (Matsuda index) was 9.4 (7.2) vs. 9.7 (6.8). Insulin secretory response was significantly enhanced in EP as compared to PP before and after adjustment for insulin sensitivity (p=0.03; standard error=14.0, P=0.01). There was no association between age, BMI in EP, or the change in BMI between EP and PP and the change in insulin secretory response.
Conclusion: We found evidence of enhancement of insulin secretory response early in pregnancy, in the absence of a change in insulin sensitivity. In light of evidence that identification and treatment of mild glucose intolerance early in pregnancy may be beneficial, larger studies of glycemic physiology in the 1st trimester are warranted.
Supported By: National Institute of Diabetes and Digestive and Kidney Diseases (K23DK113218, K24-DK094872); Robert Wood Johnson Foundation (74596)
associated with BW z-score. Similar associations were observed with CBI z-score [pre-pregnancy BMI (RC: 0.11; 95% CI: 0.06, 0.16], early GWG (RC: 0.07; 95% CI: 0.00, 0.13], glucose (RC: 0.14; 95% CI: 0.09, 0.19) and triglycerides (RC: 0.07; 95% CI: 0.02, 0.12). Maternal fasting high-density lipoprotein was negatively associated with BW z-score (RC: -0.04; 95% CI: -0.09, -0.00] and CBI z-score (RC: -0.04; 95% CI: 0.00, 0.01] but the 95% CI for the latter included the null.

Conclusions: Maternal pre-pregnancy BMI had the strongest association with BW and CBI, emphasising the importance of optimising preconception BMI. Our results also suggest potential under-recognized adverse effects of intrauterine exposure to gestational dyslipidaemia and that this may warrant clinical attention.

Nocturnal Insulin Requirements Are Higher in Pregnant Hispanic Women with Type 2 DM

JESICA C. EHRIG, AMANDA A. ALLSHOUSE, LINDA A. BARBOUR, Aurora, CO

T2DM is rapidly rising in pregnancy, especially in Hispanic women (HW). Classically, OBGYNs are taught to manage T2DM with a split dose NPH/Regular, especially if cost is a concern. OBGYN textbooks advise that 2/3 of total NPH be given in the am; 1/3 in pm based on historical data in Caucasians with T1DM. However, HW often display higher fasting glucoses (FBG) secondary to hepatic insulin resistance. We tested the hypothesis that more HW who are adequately controlled would require >50% of their NPH at night compared to non-Hispanic (NHW). All 667 pregnant women with T2DM at our county hospital from 2010–2016 were evaluated for inclusion (insulin treatment by 22 weeks ≥5 prenatal visits, and ±4 FBG≥95 mg/dl and AIC<6.5 by term). Our primary endpoint was tested with X²; differences over time with generalized linear mixed-effects modeling. Inclusion criteria were met by 102 (81 HW and 21 NHW). Mean AIC decreased from baseline to term (7.7 to 5.9; 7.2 to 5.8 respectively). By term, more HW required >50% of NPH at night (51% vs. 19%, p=0.008). Figure 1 shows each at a prenatal visit, significantly more HW required >50% NPH at night (p<0.05). Hispanic women require a higher % of NPH at night throughout gestation and at term ≥95 prenatal visits, and

Background: In the well-nourished Western populations maternal insulin concentrations (and insulin resistance) progressively increase during gestation to support fetal growth. Information in undernourished women from LMICs is scarce. We investigated serial glucose-insulin and lipid concentrations from early to late pregnancy in rural and urban Indian women, and studied their association with offspring birth weight.

Methods: Women from antenatal clinics were enrolled in early pregnancy. Fasting glucose, insulin, cholesterol and triglyceride concentrations were measured at 16, 28 and 33 weeks gestation and a 75g GTT was performed at 28 weeks gestation. GDM was diagnosed using the WHO 1999/IADPSG 2011 criteria. Demographic and anthropometric measurements were obtained, and babies were measured at birth.

Results: A total of 266 (161 rural, 95 urban) women were enrolled; they were 23 years old, 153 cm tall, and had a BMI 20.7 kg/m² at ~16 weeks gestation. Thirty nine GDM women (22 rural) were excluded from further analysis. In 217 normal glucose tolerant women, fasting plasma glucose progressively fell with increasing gestation, insulin concentrations and HOMA-IR remained similar (51%) showed a fall; total and HDL cholesterol and triglyceride concentrations increased. Urban women were older, taller and heavier, and had significantly higher glucose, insulin and HOMA-IR compared to rural women; they gained 7kg and rural women 6kg between early and late visits. Mean birth weight was 2.8kg; 39% babies were SGA and 1% LGA (INTERGROWTH). Birth weight was positively associated with maternal size (height, weight, BMI) and fasting plasma glucose concentrations. HOMA-IR was not independently associated.

Conclusion: The short and undernourished women from India failed to increase their insulin resistance with increasing gestation. This may be a novel explanation for fetal growth restriction in India and for its short term and long term sequelae, including risk of diabetes.

Association between Glyburide Dose and Adverse Neonatal Outcomes in Women with Gestational Diabetes

MAISA N. FEGHALI, STEVE CARITIS, JANET M. CATOV, CHRISTINA M. SIFFRES, Pittsburgh, PA, Oklahoma City, OK

Glyburide is used to treat women with gestational diabetes (GDM). However, recent data has demonstrated that it crosses the placenta, and concerns about the neonatal effects of glyburide treatment including fetal overgrowth and neonatal hypoglycemia persist. We sought to assess if there are subsets of women treated with glyburide who are at increased risk for adverse neonatal outcomes compared to women treated with medical nutritional therapy (MNT) alone using a retrospective cohort of 1,012 women with GDM. We collected characteristics including glucose values and pregnancy outcomes. We used bivari-
PREGNANCY—CLINICAL/EPIDEMIOLOGY

1447-P
Predicting Diabetes in the First Two Years Postpartum among Women with Recent Gestational Diabetes—The Linda-Brasil Study
CRISTINA D. CASTILHOS, RUBEN LADWIG, MICHELE DREHMER, BRUCE B. DUNCAN, CRISTINA FACANHA, MARIA I. SCHMIDT, Porto Alegre, Brazil, Fortaleza, Brazil

Background: GDM is a strong risk factor for early development of diabetes. Yet, adherence to protocols for testing at postpartum is usually low. We investigated the main predictors of diabetes up to two years post-partum among women with recent GDM participating in the LindA-Brasil cohort.

Methods: We recruited potential participants with GDM for an ongoing clinical trial of postpartum diabetes prevention, LindA-Brasil. We ascertainment diabetes by OGTT. We estimated relative risks and 95% CIs, and area under the ROC curve (AUC) for diabetes postpartum through logistic regression.

Results: We recruited 2706 women with GDM, of whom 1482 (55%) underwent OGTT testing postpartum. Among these, mean (SD) pre-pregnancy BMI was 30.2 (6.4) kg/m² and mean age, 32.0 (6.3) years; 316 (21.3%) used insulin during pregnancy, an additional 314 (21.2%) oral hypoglycemic agents (OHAs). During follow-up, 163 (11%) developed diabetes. Use of insulin during pregnancy predicted a six-fold higher crude risk of developing diabetes postpartum (RR 6.7; 95% CI 4.7-9.4) and of OHAs, a two-fold risk (RR=2.0; 95% CI 1.4-2.9). The inclusion of just these two variables yielded an AUC of 0.754; adding fasting and 2h plasma glucose at the diagnosis of GDM increased it minimally (0.810); further addition of age and pre-pregnancy BMI increased it to 0.813, and age was not statistically significant. Most incident cases used insulin (59%) or OHAs alone (20%) during pregnancy, but there was no increased risk for hypoglycemia.

Conclusion: Simple clinical or administrative information can be effectively used to prioritize screening and counseling for diabetes prevention in the initial years following pregnancy complicated by GDM.

Supported By: National Council for Scientific and Technological Development of Brazil; Eli Lilly and Company

1448-P
Association of First-Trimester Fasting Plasma Glucose with Gestational Diabetes Mellitus and Adverse Pregnancy Outcomes
PING LI, SHUO LIN, LING LI, LIPING OUYANG, JIANHUI FAN, Guangzhou, China

This study aims to evaluate the usefulness of a fasting plasma glucose (FPG) at the first trimester in predicting gestational diabetes mellitus (GDM) and the association between FPG and adverse pregnancy outcomes in Chinese women. Medical records of 2112 singleton pregnant women were collected from the third affiliated hospital of Sun Yat-Sen University, Guangzhou, China, from January 2016 to June 2017. FPG was measured at 9-13 months gestation. The incidence of GDM and large for gestational age (LGA) were 35.2% and 28.5%, respectively.

Methods: 2112 pregnant women were recruited for an ongoing clinical trial of postpartum diabetes prevention, LindA-Brasil. We ascertained diabetes by OGTT. We estimated relative risks and 95% CIs, and area under the ROC curve (AUC) for diabetes postpartum through logistic regression.

Results: We recruited 2706 women with GDM, of whom 1482 (55%) underwent OGTT testing postpartum. Among these, mean (SD) pre-pregnancy BMI was 30.2 (6.4) kg/m² and mean age, 32.0 (6.3) years; 316 (21.3%) used insulin during pregnancy, an additional 314 (21.2%) oral hypoglycemic agents (OHAs). During follow-up, 163 (11%) developed diabetes. Use of insulin during pregnancy predicted a six-fold higher crude risk of developing diabetes postpartum (RR 6.7; 95% CI 4.7-9.4) and of OHAs, a two-fold risk (RR=2.0; 95% CI 1.4-2.9). The inclusion of just these two variables yielded an AUC of 0.754; adding fasting and 2h plasma glucose at the diagnosis of GDM increased it minimally (0.810); further addition of age and pre-pregnancy BMI increased it to 0.813, and age was not statistically significant. Most incident cases used insulin (59%) or OHAs alone (20%) during pregnancy, but there was no increased risk for hypoglycemia.

Conclusion: Simple clinical or administrative information can be effectively used to prioritize screening and counseling for diabetes prevention in the initial years following pregnancy complicated by GDM.

Supported By: National Council for Scientific and Technological Development of Brazil; Eli Lilly and Company

1449-P
Free Thyroxin T4 in Early Pregnancy and Risk of Gestational Diabetes Mellitus
PING LI, SHUO LIN, LING LI, LIPING OUYANG, JIANHUI FAN, Guangzhou, China

Our study aims to evaluate the correlations between thyroid hormone levels in early pregnancy and the incidence of gestational diabetes mellitus (GDM). A total of 2112 pregnant women were recruited from our hospital, Guangzhou, China, from June 2016 to June 2017. Fasting plasma glucose (FPG), Thyrotropin (TSH), free T4 (FT4), and thyroid peroxidase antibody (TPO-Ab) were measured at 9-14 weeks gestation (first trimester) and 24-28 weeks gestation. Diagnosis of GDM was made by the IADPSG guideline (2010). All subjects had median age of 30 years (interquartile range:27-34 years). Two hundred and twenty four subjects (10.6%) were diagnosed as GDM. GDM women had older age and higher FPG (P<0.05). The level of free T4 (FT4) in GDM women was similar than that in non-GDM women (1.64±0.32 pmol/L and 1.60±0.46 pmol/L, respectively, P=0.152). No difference was observed in the levels of TSH and TPO-Ab between GDM women and non-GDM women (all P>0.05). The prevalence of GDM in subjects among different quartiles of FT4 levels were 11.3%, 11.5%, 9.5% and 9.5% from the first to fourth quartile (P=0.429; p=2.765). By using logistic regression, FT4 in the first trimester odds ratios for GDM were not significant: OR 0.970 [95% CI 0.931-1.011] (unadjusted) and 0.960[95% CI 0.920-1.002] (adjusted for age, TSH, TPO-Ab). Our results indicated the level of FT4 in the first trimester may not have strong correlation with incidence of GDM.

Supported By: Science and Technology Planning Project of Guangdong Province, China (2017A020215026), Medical Scientific Research Foundation of Guangdong Province, China (A2017314)

1450-P
Risk Factors for Pregnancy Hypertensive Disorders in a Cohort of Women with Pregestational Diabetes
MARIA LUCIA R. OPPERMAN, JANINE ALESSI, VÂNIA N. HIRAKATA, DANIELA WIEGAND, ANGELA J. REICHELT, Porto Alegre, Brazil

Background: Pregestational diabetes (PGD) is associated with increased incidence of pregnancy hypertensive disorders (PHD).

Aim: to describe incidence and risk factors for PHD in a retrospective cohort of PGD women.

Methods: Women were evaluated at a specialized prenatal care facility. PHD comprised preeclampsia and gestational hypertension. Gestational
White Coat Hypertension in Early Pregnancy Is Prevalent in Women with Type 1 and Type 2 Diabetes

MARIANNE VESTGAARD, BJØRG ASSBJØRNSDOTTIR, LENE RINGHOLM, DORTE M. JENSEN, LISE LOTTE TORVIN ANDERSEN, PETER DAMM, ELISABETH R. MATHIESEN, Copenhagen, Denmark; Gentofte, Denmark; Odense, Denmark.

Aim: Verifying the diagnosis of hypertension in pregnancy by home blood pressure (BP) or 24-h BP measurements is recommended (ACOG, 2013) to avoid over-treatment of white coat hypertension. In pregnancy a threshold of 140/90 mmHg measured by office BP is normally used, but in our center, we use a threshold of ≥135/85 mmHg for antihypertensive therapy in women with diabetes. The prevalence of white coat hypertension in pregnant women with diabetes is unknown. We explored the prevalence of white coat hypertension in early pregnancy in women with type 1 (T1DM) and type 2 (T2DM) diabetes.

Methods: Home BP was measured for 3 days (18 measurements in total) at median 67 gestational days (range 33-139), within a week of office BP measurement. The women were divided in groups: treated hypertension, white coat hypertension (office BP ≥135/85 mmHg and mean home BP <130/80 mmHg), true new-onset hypertension (office BP ≥135/85 mmHg and mean home BP ≥130/80 mmHg), masked hypertension (office BP <135/85 mmHg and home BP ≥130/80 mmHg) and normotension (office BP <135/85 mmHg and mean home BP <130/80 mmHg).

Results: In total 178 (72%) out of 244 consecutive pregnant women with diabetes included were: 107 women with T1DM and 71 women with T2DM with mean age 31±5 and 34±4 years and mean BMI 27±6 and 34±5 kg/m², respectively. Treated hypertension was present in 11 (6%). In total 20/27 (74%) of the remaining women with hypertension measured by office BP ≥135/85 mmHg had white coat hypertension (85% (12/14) of women with T1DM and 62% (8/13) in women with T2DM). Among women with office BP ≥140/90 mmHg 8/9 (89%) had white coat hypertension (home BP <135/85 mmHg). True new onset hypertension was seen in 7 (4%). One woman had masked hypertension and the remaining 131 (78%) were normotensive.

Conclusion: White coat hypertension in early pregnancy is prevalent in women with T1DM and T2DM. These data support routine home BP measurement before initiating antihypertensive therapy in this population.

Supported By: Rigshospitalet Research Foundation

Management of GCK-MODY in Pregnancy—Does Clinical Practice Follow Current Recommendations?

LAURA T. DICKENS, LISA R. LETOURNEAU, LOUIS H. PHILIPSON, SIRI ATMA W. GREELEY, ROCHELLE N. NAYLOR, Chicago, IL.

Recommendations for management of GCK-MODY during pregnancy are based on fetal genotype. Women with GCK-MODY should not be treated with insulin prior to conception and insulin should not be given if normal fetal growth is observed. Women should be treated with insulin if fetal ultrasound monitoring starting at 26 weeks shows macrosomia, suggesting the fetus is wild type for the GCK gene. There is limited data about management of GCK-MODY in pregnancy.

The aim of this study was to examine clinical management and pregnancy outcomes amongst women with a known diagnosis of GCK-MODY. A survey was distributed via Redcap to 94 women >/= 18 years enrolled in the University of Chicago Monogenic Diabetes Registry. All or part of the survey was completed by 59% of women.

GCK-MODY diagnosis was known at the time of pregnancy for 14 women with a total of 19 pregnancies, including 2 women who were currently pregnant. There were 13 term births and 3 premature births. Glucose-lowering therapy was used preconceptionally in 33% of cases, including insulin use in 3 women. Insulin was started in 7 pregnancies; in 4 cases the fetus measured normal for dates and in 3 cases measured large. Insulin was started between 5-32 weeks (average 16.4 weeks). Insulin treatment was not started in 1 pregnancy where the baby measured large for dates and early induction was required. This offspring was WT for GCK.

In our study, contrary to current recommendations, one-third of pregnancies were treated with glucose-lowering medication prior to pregnancy, including insulin. Insulin initiation occurred early in gestation (average 18.4 weeks), rather than being based on fetal size on ultrasound monitoring. These observations suggest that for many pregnancies affected by GCK-MODY, management does not reflect current guidelines. Further studies to confirm the safety and efficacy of the current recommendations may improve provider confidence in deferring insulin treatment in cases where ultrasound monitoring shows normal fetal growth.

Supported By: National Institutes of Health (K23DK114584)
Design and methods: We carried out a retrospective study of 92 singleton pregnancies in 79 T1D Caucasian patients, 59 of whom were OP and 33 UP who attended our Diabetes and Pregnancy Unit since 2013 to 2017. In each of the groups were evaluated the pre-pregnancy characteristics, in each trimester and the MFO. Preconception A1C goal was ≥5% without exceeding 6.5% with a glycemic target of a fasting glucose between 70-95mg/dl and 1 hour postprandial 90-140 mg/dl.

Results: Both groups did not differ by age: 34 (36-43) vs. 31 (21-42) years, T1D duration: 17 (2) vs. 14 (1-31) years and pregestational BMI. Pre-gestancy A1C OP vs. UP was 5% (5.1-6.0) vs. 7.4% (6.8-10.1) P<.001. During the first trimester: 5.7% (5.2-6.5) vs. 6.6% (5.7-7.8) P<.01, in the 2nd: 5.8% (4.8-6.4) vs. 6.3% (5.3-7.0) and in the 3rd: 5.9% (5.0-6.5) vs. 8.2% (5.2-6.9) without differences in weight gain and preeclampsia development. OP vs. UP patients had a 27.1% of cesarean delivery vs. 33.3% (p<.05) with no differences in preterm and intramental delivery. Regarding fetal outcomes the neonatal birth weight was 3270 gr (2198-4280) vs. 3370 gr (1200-4870) with a higher percentage in the UP of larger for gestational age newborns (15.2% vs. 3.3% p>.05), malformations (1.6% vs. 15.1% p>.05) and hypoglycemia (6.7% vs. 27.2% p>.05). No differences in macrosomia, small for gestational age, shoulder dystocia, jaundice or respiratory distress.

Conclusion: In women with preexisting T1D preconceptional counseling and glycemic optimization represent a fundamental step towards improved pregnancy outcomes. Pre-pregnancy A1C <6% and during the 1st trimester seems to decrease the risk of adverse outcomes.

### 1455-P

**Medical Nutrition Therapy for Gestational Diabetes Mellitus (GDM) Based on Mediterranean Diet Principles**

ALEJANDRA DURAN, CARLA ASSAF-BALUT, NURIA GARCIA DE LA TORRE, MANUEL FUENTES, ELENA BORDIU, LAURA DEL VALLE, ANA M. BARABASH, MARTIN OUESTA, MIGUEL A. RUBIO, AUTONO L. CALLE, Madrid Spain

Background: Medical nutrition therapy (MNT) is the first-line therapy to achieve glycemic control in women with gestational diabetes mellitus (GDMw). It has been associated with better pregnancy outcomes. Whether MNT can make pregnancy outcomes like women without GDM remains unknown.

Objective: To assess if a Mediterranean-diet-based medical nutrition therapy (MNT) facilitates near-normoglycemia determined by HbA1c levels at 36-38 gestational weeks in GDMw, and observe its effects on adverse pregnancy outcomes.

Study Design: A sub-analysis of the St Carlos GDM Prevention Study. It was conducted between January-December 2015 in the Hospital Clinico San Carlos (Madrid, Spain). One thousand consecutive normoglycemic women were included before 12th gestational weeks, and 874 included in the final analysis: 177 were diagnosed with GDM (ADQPSG criteria) and 697 had normal glucose tolerance. GDMw received Mediterranean diet-based MNT, with a daily intake of ≤40 ml extra-virgin olive oil and a handful of nuts (mainly pistachios).

Results: GDMw had higher HbA1c levels, fastinG insulin and HOMA-IR at 24-28 gestational weeks as compared with NGT. At 36-38 gestational weeks these values became similar. Insulin therapy was necessary in 26.6% with no differences in preterm and intramental delivery. Regarding fetal outcomes the neonatal birth weight was 3270 gr (2198-4280) vs. 3370 gr (1200-4870) with a higher percentage in the UP of larger for gestational age newborns (15.2% vs. 3.3% p>.05), malformations (1.6% vs. 15.1% p>.05) and hypoglycemia (6.7% vs. 27.2% p>.05). No differences in macrosomia, small for gestational age, shoulder dystocia, jaundice or respiratory distress.

Conclusion: In women with preexisting T1D preconceptional counseling and glycemic optimization represent a fundamental step towards improved pregnancy outcomes. Pre-pregnancy A1C <6% and during the 1st trimester seems to decrease the risk of adverse outcomes.

### 1455-P

**Medical Nutrition Therapy for Gestational Diabetes Mellitus (GDM) Based on Mediterranean Diet Principles**

ALEJANDRA DURAN, CARLA ASSAF-BALUT, NURIA GARCIA DE LA TORRE, MANUEL FUENTES, ELENA BORDIU, LAURA DEL VALLE, ANA M. BARABASH, MARTIN OUESTA, MIGUEL A. RUBIO, AUTONO L. CALLE, Madrid Spain

Background: Medical nutrition therapy (MNT) is the first-line therapy to achieve glycemic control in women with gestational diabetes mellitus (GDMw). It has been associated with better pregnancy outcomes. Whether MNT can make pregnancy outcomes like women without GDM remains unknown.

Objective: To assess if a Mediterranean-diet-based medical nutrition therapy (MNT) facilitates near-normoglycemia determined by HbA1c levels at 36-38 gestational weeks in GDMw, and observe its effects on adverse pregnancy outcomes.

Study Design: A sub-analysis of the St Carlos GDM Prevention Study. It was conducted between January-December 2015 in the Hospital Clinico San Carlos (Madrid, Spain). One thousand consecutive normoglycemic women were included before 12th gestational weeks, and 874 included in the final analysis: 177 were diagnosed with GDM (ADQPSG criteria) and 697 had normal glucose tolerance. GDMw received Mediterranean diet-based MNT, with a daily intake of ≤40 ml extra-virgin olive oil and a handful of nuts (mainly pistachios).

Results: GDMw had higher HbA1c levels, fastinG insulin and HOMA-IR at 24-28 gestational weeks as compared with NGT. At 36-38 gestational weeks these values became similar. Insulin therapy was necessary in 26.6% of GDMw. Rates of macrosomia, large-for-gestational-age, pregnancy-induced hypertensive disorders, prematurity and c-sections were similar between groups. Crude RR analysis showed that GDMw had a higher risk of insulin therapy was necessary in 26.6% of GDMw. Rates of macrosomia, large-for-gestational-age, pregnancy-induced hypertensive disorders, prematurity and c-sections were compared. Mean maternal booking BMI was 38, 37.6 and 36 kg/m² (p<0.01) and mean maternal age was 34.7, 34.1 and 33.3 years in groups 1,2 and 3 respectively (p<.04). Rates of PIH PET APH PPH and CS were similar between groups. Glycaemic control prior to delivery was better in women in group 1 compared to groups 2 and 3 (HbA1C 37.2 vs. 38.4 gr. 39 mmol/mol; P = 0.02). Infant birth weight was lower in group 1 compared to groups 2 and 3 (3545 vs. 3645 vs. 3703g; p<0.01) Rates of HGA, macrosomia. SGA and prematurity (<37 gestational weeks) were similar between groups. Rates of neonatal hypoglycemia were less in group 1 compared to groups 2 and 3; (2.1% vs. 14.3% vs. 4%; p<0.01), while all other morbidity outcomes were similar between groups. Gestational weight change for GDM women treated with insulin below that recommended by the IOM appears safe. In addition, it is associated with better maternal glycaemic control and lower infant birth weight.

### 1457-P

**Intensive Metabolic Control of T1D Pregnant Women in CSII vs. MDI—A Retrospective Analysis**

SARA PARRETTINI, IRENE GIARDINA, FRANCESCA CARDINI, ELISABETTA TIRONI, Perugia, Italy

Diabetes-complicated pregnancy requires intensive gluco-metabolic monitoring. There is no clear evidence that insulin pump therapy (CSII) is superior to multiple daily injections with insulin analogs (MDI) in achieving tight glycemic control. We conducted a retrospective analysis on 72 (69 single and 3 twins) T1D pregnant women, followed at the Diabetics and Pregnancy Unit University Hospital, Perugia) since the first weeks of gestation or before conception. Maternal metabolic parameters (HbA1c, mean BG, weight gain, prandial and basal insulin needs and percentage increase in insulin requirements, ICHO ratio) at conception, and each trimester, were assessed. Finally, neonatal outcomes (birth weight, newborn age, neonatal complications-malformations incidence) were analyzed. We compared the data with regard to applied regimens (CSII vs. MDI). 28 women were on CSII (38.8%) and 44 on MDI therapy, with mean HbA1c at conception of 7.1 ± 0.7% vs. 7.2 ± 1.2%, respectively (P>0.05). Women who received pre-conception counseling (56% of CSII women vs. 13% of MDI), showed significantly lower HbA1c at conception (6.7 ± 0.6 vs. 7.3 ± 1.1, p<0.05). Disease duration, previous abortion rate and prevalence of chronic complications (class D-G, White classification) were significantly higher in CSII group. In single pregnancies, no significant differences were observed, in CSII vs. MDI, as far as HbA1c, insulin (IU/Kg), percentage increase of insulin requirements, ICHO ratio, weight increase, gestation term, birth weight, prevalence of maternal and neonatal complications were concerned (p>0.05). CSII was not proved superior to MDI in the management of pregnancy, in terms of neither maternal insulin requirements nor of maternal-fetal outcomes. Intensive management of diabetic pregnancy ensures stringent glycemic control, regardless of treatment with CSII or MDI. The choice of treatment modality should be targeted on pre-gestational and individual parameters.

### 1458-P

**Treatment of Gestational Diabetes and Offspring Early Childhood Growth**

MAISA N. FEGHALL, JACQUELINE ATLAissenschaftlich, STEVE CARITIS, JANET M. CATOV, CHRISTINA M. SCIFRES, Pittsburgh, PA, Oklahoma City, OK

Gestational diabetes mellitus (GDM) is associated with childhood obesity and there is concern that glyburide is associated with macrosomia and perhaps childhood overweight.

We sought to examine if GDM treatment type is associated with differences in early childhood growth using a retrospective cohort of 952 women with GDM and their offspring. We collected pregnancy and breastfeeding data as well as height and weight through age 5. We used bivariate and multivariable regression analyses to compare early childhood growth among maternal GDM treatment.

Treatment was divided into medical nutritional therapy (MNT), glyburide, and insulin. LGA at birth was more common in offspring exposed to insulin
and glyburide compared to those treated with MNT (11.7 vs. 9.2 vs. 5.7%, p=0.03). Weight or BMI at 6 months, 1, 2 and 3 years of age did not differ among children born to women with different GDM treatments. GDM treatment type was not predictive of weight or associated with a higher risk for BMI >85th percentile at age 2 or 3 years after adjusting for covariates including gender, age at recorded weight, birth weight category, pre-pregnancy weight gain, gestational age, and breastfeeding.

Our findings suggest that maternal pre-pregnancy BMI but not GDM treatment is associated with variations in early childhood growth. Further studies are needed to determine if these findings persist beyond 3 years of age and to explore differences in body composition.

### Table

<table>
<thead>
<tr>
<th>Factor</th>
<th>Preexisting Rate (n=134)</th>
<th>Ref</th>
<th>Beta Coefficient (95% CI)</th>
<th>P</th>
<th>Beta Coefficient (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight category</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AGA</td>
<td>Ref</td>
<td>n/a</td>
<td>-0.16 (-0.48-0.15)</td>
<td>0.30</td>
<td>-0.13 (-0.50-0.28)</td>
<td>0.50</td>
</tr>
<tr>
<td>SGA</td>
<td>Ref</td>
<td>n/a</td>
<td>-0.39 (-0.74-0.02)</td>
<td>0.001</td>
<td>-0.39 (-0.74-0.02)</td>
<td>0.001</td>
</tr>
<tr>
<td>LGA</td>
<td>Ref</td>
<td>n/a</td>
<td>-0.50 (-0.85-0.15)</td>
<td>0.001</td>
<td>-0.50 (-0.85-0.15)</td>
<td>0.001</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDM</td>
<td>0.35 (0.22-0.51)</td>
<td>0.001</td>
<td>0.17 (0.02-0.31)</td>
<td>0.026</td>
<td>0.17 (0.02-0.31)</td>
<td>0.026</td>
</tr>
<tr>
<td>Prepregnancy BMI</td>
<td>0.16 (0.04-0.27)</td>
<td>0.003</td>
<td>0.12 (0.02-0.22)</td>
<td>0.029</td>
<td>0.12 (0.02-0.22)</td>
<td>0.029</td>
</tr>
<tr>
<td>Pregnancy weight gain</td>
<td>0.003 (0.003-0.003)</td>
<td>0.015</td>
<td>0.08 (0.011-0.061)</td>
<td>0.004</td>
<td>0.08 (0.011-0.061)</td>
<td>0.004</td>
</tr>
<tr>
<td>Any breastfeeding</td>
<td>-0.09 (-0.06-0.02)</td>
<td>0.041</td>
<td>-0.03 (0.017-0.034)</td>
<td>0.030</td>
<td>-0.03 (0.017-0.034)</td>
<td>0.030</td>
</tr>
</tbody>
</table>

Supported By: National Institutes of Health

**Maternal Diabetes during Pregnancy and Early Childhood Obesity—A Population-Level Analysis**

SAMANTHA L. BOWKER, ANAMARIA SAVI, ROSEANNE O. YEUNG, EDMOND A. RYAN, PADMMA KAUL, EDMONTON, AB, Canada

We examined the association between maternal diabetes status (preexisting diabetes mellitus [pre-DM], gestational diabetes mellitus [GDM], and no DM) during pregnancy and overweight or obesity status of the offspring in early childhood (4-6 years). Immunization records, containing height and weight at the time of preschool vaccination for children born between Jan 2005-Aug 2013 in Alberta, Canada were linked with the following: 1) maternal hospitalization and outpatient records prior to delivery; and 2) registry data containing birth weight, parity, and gestational age. World Health Organization (WHO) criteria were used to categorize children as overweight or obese. Our cohort had 91,382 live births from 68,457 mothers. Rates of pre-DM, GDM and no-DM were 8.8%, 6.2%, and 93.0%, respectively (Table). Childhood overweight/obesity rates were significantly higher among women
GLP-1 Receptor Agonist Liraglutide Increased IVF Pregnancy Rates in Obese Women with PCOS and Previous Poor Response to First-Line Reproductive Treatments

ANDREJ JANEZ, MOJCA JENSTERLE, Ljubljana, Slovenia

Objective: GLP-1 has been investigated in regulation of reproductive system in animal models. Current observations suggest that it directly regulates kisspeptin and GnRH expression and that ovaries express GLP-1 mRNA.

Aim: To evaluate the impact of low dose liraglutide in combination with metformin compared to metformin alone on IVF pregnancy rate (PR) and cumulatively PR (IVF and spontaneous) in infertile obese women with PCOS who had been previously poor responders regarding weight reduction with lifestyle modification and resistant to first line reproductive treatments.

Design/Participants/Methods: A prospective randomized open-label study was conducted with 28 infertile obese PCOS patients (aged 31.0±4.75 years, BMI 36.7±3.5 kg/m², mean ± SD). They were assigned to metformin (MET) 1000 mg BID or combined MET 1000 mg BID and low dose liraglutide 1.2 mg OD (0.5 mg SC) for 12 weeks. Ovarian stimulation protocol was started after 4-week medication free period.

Results: Patients in MET lost on average 7.0±6.0 kg (P<0.001) compared with MET+LIR 7.5±3.9 kg (P<0.001). MET and MET+LIR groups showed statistically significant difference in weight loss, with no significant between-patient differences in pre-DM or GDM, than with no-DM. After adjustment, both GDM and pre-DM were associated with a higher likelihood of having an overweight/obese child. Breast feeding data were available for 63,374 children. A higher proportion of GDM and pre-DM babies were not breast fed, which was also associated with a higher risk of childhood obesity. The impact of maternal diabetes on offspring weight continues beyond birth to early childhood. This association may be further exacerbated by breast feeding challenges in women with diabetes.

Supported By: Canadian Institutes of Health Research

Plasma Metabolomics Reveal Novel Metabolites in Early Pregnancy in Association with Gestational Diabetes Risk

CUILIN ZHANG, YEN-CHEN ANNE FENG, OLIVER FIEHN, MICHAEL Y. TSAI, YEYI ZHU, PAUL ALBERT, LIMING LIANG, Bethesda, MD, Boston, MA, Davis, CA, Minneapolis, MN, Oakland, CA

Although metabolomics may shed light on the pathophysiology of glucose metabolism in pregnancy, systematic studies on their roles in the development of gestational diabetes (GDM) are sparse. We aimed to prospectively investigated metabolomics (both targeted and non-targeted) and GDM risk in a matched case-control study of 107 GDM and 214 non-GDM women in a multi-racial cohort. GDM diagnosis was based on Carpenter and Coustan Criteria. Twenty-two amino acids were quantified using plasma collected at gestational weeks (GW) 10-14, 15-26, 23-31, and 33-39. In addition, 331 primary metabolites were quantified by GC-TOF-MS as a part of our non-targeted approach. Adjusted odds ratios (aORs) of GDM related to metabolites (in quartiles (Q)) were estimated using conditional logistic regression after adjusting for major GDM risk factors including BMI. The present report focuses on findings using blood samples in early pregnancy 10-14GW. Alanine in GW 10-14 were higher in GDM women than controls (mean: 30.5 vs. 27.6 umol/dl) and were positively related to GDM risk; aORs across increasing Qs were 1.00, 1.69, 2.86, 3.05, (P for trend =0.020). By contrast, asparagine and glycine were significantly lower in GDM women, and were inversely related to GDM risk; aORs across increasing Qs were 1.00, 0.92, 0.74, and 0.48 (P for trend = 0.045) for asparagine and 1.00, 0.42, 0.24, and 0.24 (P <0.001) for glycine. In addition, among primary metabolites from the non-targeted approach, isocitric acid levels were positively related to GDM risk; aORs across increasing Qs were 1.00, 1.30, 1.04, 2.32 (P for trend = 0.002). Furthermore, two unknown metabolites were strongly and inversely associated with GDM risk (aORs were 1.00, 0.52, 0.18, 0.11, and 1.00, 0.33, 0.12, 0.06 respectively; both P <10^-4).

Conclusion: Our study revealed several novel metabolites that may be implicated in the early pathogenesis of GDM, which might provide new etiological insight into the development of GDM.

GLP-1 Receptor Agonist Liraglutide Increased IVF Pregnancy Rates in Obese Women with PCOS and Previous Poor Response to First-Line Reproductive Treatments

ANDREJ JANEZ, MOJCA JENSTERLE, Ljubljana, Slovenia

Objective: GLP-1 has been investigated in regulation of reproductive system in animal models. Current observations suggest that it directly regulates kisspeptin and GnRH expression and that ovaries express GLP-1 mRNA.

Aim: To evaluate the impact of low dose liraglutide in combination with metformin compared to metformin alone on IVF pregnancy rate (PR) and cumulatively PR (IVF and spontaneous) in infertile obese women with PCOS who had been previously poor responders regarding weight reduction with lifestyle modification and resistant to first line reproductive treatments.

Design/Participants/Methods: A prospective randomized open-label study was conducted with 28 infertile obese PCOS patients (aged 31.0±4.75 years, BMI 36.7±3.5 kg/m², mean ± SD). They were assigned to metformin (MET) 1000 mg BID or combined MET 1000 mg BID and low dose liraglutide 1.2 mg OD (0.5 mg SC) for 12 weeks. Ovarian stimulation protocol was started after 4-week medication free period.

Results: Patients in MET lost on average 7.0±6.0 kg (P<0.001) compared with MET+LIR 7.5±3.9 kg in COMBI group (P<0.001), with no significant between-
treatment difference (P=0.103). All treatment interventions resulted in significant reduction of visceral adipose tissue as assessed by DXA and reduction of HOMA-IR (p<0.001), with no significant difference regarding the treatment employed. After intervention, PR per ET was significantly higher in COMBI (85.7%) compared with MET (28.6%) (P=0.03). Moreover, cumulative PR in time frame of 12 months in COMBI was 69.2% compared to 35.7% in MET.

Conclusion: Short-term preconception intervention with low dose liraglutide as an add on to metformin was superior to metformin alone in increasing PR per ET and cumulative PR in infertility obese PCOS, despite comparable weight reduction in both arms. Potential direct crossstalk between GLP-1 and reproductive system needs further exploration.

EPIDEMIOLOGY—AGING

1466-P

Relationship between Executive Functioning and Glycemic Controls in Patients with Type 2 Diabetes

TAICHI MINAMI, MASAYO YAMADA, YUYURO ITI, RYUTARO FURUTA, SHO KATSURAGAWA, SAKIKO TERUI, TOMODAKI AKIYAMA, FUTUKI MINAGAWA, YASUO TERAUCHI, Osaka, Japan

Type 2 diabetes (T2D) is a risk factor for Alzheimer’s disease. Executive dysfunction occurs in otherwise cognitively normal patients with T2D. To assess executive function, we investigated the relationship between executive function and glycemic controls using verbal fluency (VF) tests. The present study enrolled 130 patients with T2D (age, ≥60; including 11 patients with dementia) and excluded stroke survivors. Their HbA1c levels were recorded every ≤12 weeks for ≤5 years. All patients underwent VF tests. We analyzed the correlation between VF z-scores (standardized total scores) and glycemic control values (time-weighted average and maximum HbA1c levels for the past 5 years), or disease durations. As controls, we also investigated the relationships between stages of diabetic retinopathy (NDR/NPDR/PD) and past glycemic controls. The mean patient age was 74.7 years, the mean HbA1c at the baseline was 7.5%, median duration of education was 12 years, and mean disease duration was 18.3 years. Significant correlates for VF z-scores were age, years of education, and dementia in addition to glycemic control values. VF z-scores tended to correlate with average HbA1c levels, and significantly correlated with maximum HbA1c levels, for the past 5 years. The relationships between VF z-scores and maximum HbA1c levels remained significant after adjusting for age, years of education, and dementia. Generally, VF z-scores were strongly associated with maximum HbA1c levels for longer observation periods, i.e., VF z-scores correlated with maximum HbA1c levels for the past 5 years, best compared with maximum HbA1c levels for the past 4 years. As controls, diabetic retinopathy stages were also associated with average and maximum HbA1c levels. The diabetes duration was associated with diabetic retinopathy stages strongly, but not with VF z-scores. These results suggest that executive dysfunction may be caused by metabolic mechanisms other than diabetic retinopathy.

1467-P

Serum Sclerostin, Body Composition, and Physical Function in Postmenopausal Women with Type 2 Diabetes

FRANCISCO BANDEIRA, CONCEICAO D. CHAVES, MARIA ELBA BANDEIRA FARIAS, LARISSA B. PIMENTEL, LEONARDO FARIAS, Recife, Brazil; Natal, Brazil

Background: Sclerostin (SCL), produced mainly by osteocytes, inhibits the Wnt pathway and bone formation, and may be influenced by skeletal muscle mass. Serum Sclerostin is high in PMW with T2DM, as well as the presence of sarcopenia. Since SCL is also involved in vascular endothelial remodeling and inflammation, adiposopathy may also be related to high SCL in T2DM.

Conclusion: Serum sclerostin is high in PMW with T2DM, as well as the presence of sarcopenia. Since SCL is also involved in vascular endothelial remodeling and inflammation, adiposopathy may also be related to high SCL in T2DM.

Figure.

Supported By: Arab Society for Pediatric Endocrinology and Diabetes

1468-P

Frailty and Health Care Utilization among Community-Dwelling Older Patients with Diabetes Mellitus

SHIVANI PRIYADARSHNI, SRUTHI NELLIUR, ZUBAIR RAHAMAN, MICHAEL J. MINTZER, STUTI DANG, WILLY MARCOS VALENCIA, JORGE G. RUIZ, Miami, FL

Frailty is a state of vulnerability to stressors resulting in higher morbidity, mortality and healthcare utilization in older adults. Frailty impact on healthcare utilization in patients with T2DM is not well characterized. The aim of this study was to determine in a community cohort of older patients (85 years and older) with type 2 diabetes mellitus (T2DM) whether frailty is associated with healthcare utilization. Community dwelling Veterans with T2DM underwent frailty assessment with the validated 5-item FRAIL Scale (frail ≥3, pre-frail 1-2, robust 0 points) between January 2016 and December 2017. At one year follow-up, we aggregated data on patients with a least one primary care visit, hospitalization and/or ER visit. Binomial logistic regression was used to examine the association between frailty and emergency department (ED) visits or hospitalizations. Among 868 patients (mean age 74 ± 7 years, 58% men), 31% were robust, 36% prefrail, and 33% frail. Over a mean follow-up period of 274 ± 90 days, 1221 primary care visits, 396 ED visits, and 219 hospitalizations occurred. Frailty was associated with an increased risk for ED visits (odds ratio: 1.73, 95% CI 1.19-2.52) and an increased risk for hospitalizations (odds ratio: 3.88, 95% CI 1.18-12.22). The population-attributable risk associated with frailty was 51% for ED visits and 40% for hospitalizations.

In conclusion, frailty is a strong predictor of ED visits and hospitalizations in older patients with T2DM. As frailty is a potentially treatable condition, it should be part of the clinical evaluation of patients with T2DM.

1469-P

Association between Dementia and Glycemic Control in Elderly Patients

TAKUMA YASUDA, SEJI MURU, HARUKA FUJITA, MASAKI FUJIMURA, TOSHINOBU HATOKO, EISAI KI ORI, SHIN YONEMITSU, Osaka, Japan

Background: The goals of glycemic control based on their cognitive function are recommended for elderly patients. However, the recommendation of the glycemic control is different among the associations. That is, IDF and the Japan Diabetes Society set lower limit of HbA1c and ADA doesn’t. Moreover, there is not a clear course of treatments for elderly diabetics with dementia.

Methods: We retrospectively assessed the correlation between blood glucose management and cognitive function of 616 outpatients aged 65 years or older who visited our hospital from March 14 to April 30, 2017. HbA1c, blood glucose level, and therapeutic agents were obtained from medical records. Cognitive function was evaluated with Dementia Assessment Sheet for Community-based Integrated Care System 21-items (DASC-21), which the Japan Diabetes Society and the Japan Geriatrics Society approve. The patients were allocated to three categories based on cognitive function (normal function: I, mild dementia: II, moderate and severe dementia: III), and two categories based on therapeutic agents (not using insulin, SU, or glinide: A, using insulin, SU, and/or glinide: B).

ADA-Supported Research
Moderated Poster Discussion
treatment difference (P=0.103). All treatment interventions resulted in significant reduction of visceral adipose tissue as assessed by DXA and reduction of HOMA-IR (p<0.001), with no significant difference regarding the treatment employed. After intervention, PR per ET and cumulative PR in infertile obese PCOS, despite comparable weight reduction in both arms. Potential direct crossstalk between GLP-1 and reproductive system needs further exploration.

Conclusion: Serum sclerostin is high in PMW with T2DM, as well as the presence of sarcopenia. Since SCL is also involved in vascular endothelial remodeling and inflammation, adiposopathy may also be related to high SCL in T2DM.

Figure. Percentage of patients with sarcopenia and elevated serum sclerostin levels

Supported By: Arab Society for Pediatric Endocrinology and Diabetes

Research Supported By: Arab Society for Pediatric Endocrinology and Diabetes

Association between Dementia and Glycemic Control in Elderly Patients

TAKUMA YASUDA, SEIJI MURU, HARUKA FLUITA, MASAKI FUJIMURA, TOMONORI HATOKO, ESAKU MORI, SHIY YONEMITSU, Chiba, Japan

Background: The goals of glycemic control based on their cognitive function are recommended for elderly patients. However, the recommendation of the glycemic control is different among the associations. That is, IDF and the Japan Diabetes Society set lower limit of HbA1c and ADA doesn’t. Moreover, there is not a clear course of treatments for elderly diabetics with dementia.

Methods: We retrospectively assessed the correlation between blood glucose management and cognitive function of 616 outpatients aged 65 years or older who visited our hospital from March 14 to April 30, 2017. HbA1c, blood glucose level, and therapeutic agents were obtained from medical records. Cognitive function was evaluated with Dementia Assessment Sheet for Community-based Integrated Care System 21-items (DASC-21), which the Japan Diabetes Society and the Japan Geriatrics Society approve. The patients were allocated to three categories based on cognitive function (normal function; I, mild dementia; II, moderate and severe dementia; III), and two categories based on therapeutic agents (not using insulin, SU, or glinide: A, using insulin, SU, and/or glinide: B).

In conclusion, frailty is a strong predictor of ED visits and hospitalizations in older patients with T2DM. As frailty is a potentially treatable condition, it should be part of the clinical evaluation of patients with T2DM.

Conclusion: Frailty is a state of vulnerability to stressors resulting in higher morbidity, mortality and healthcare utilization in older adults. Frailty impact on healthcare utilization in patients with T2DM is not well characterized.

The aim of this study was to determine in a community cohort of older patients (65 years and older) with type 2 diabetes mellitus (T2DM) whether frailty is associated with healthcare utilization. Community dwelling Veterans with T2DM underwent frailty assessment with the validated 5-item FRAIL Scale (frail ≥ 3, pre-frail 1–2, robust 0–2 points) between January 2016 and December 2017. At one year follow-up, we aggregated data on patients with at least one primary care visit, hospitalization and/or ER visit. Binomial logistic regression was used to examine the association between frailty and emergency department (ED) visits or hospitalizations. Among 868 patients (mean age 74 ± 7 years, 58% women, 31% were robust, 36% prefrail, and 33% frail) over a mean follow-up period of 274 ± 90 days, 1221 primary care visits, 396 ED visits, and 219 hospitalizations occurred. Frailty was associated with an increased risk for ED visits (odds ratio: 1.73, 95% CI 1.19-2.52) and an increased risk for hospitalizations (odds ratio: 3.88, 95% CI 1.18-12.22). The population-attributable risk associated with frailty was 51% for ED visits and 40% for hospitalizations.

In conclusion, frailty is a strong predictor of ED visits and hospitalizations in older patients with T2DM. As frailty is a potentially treatable condition, it should be part of the clinical evaluation of patients with T2DM.

Study background: Sclerostin (SCL), produced mainly by osteocytes, inhibits the Wnt pathway and bone formation, and may be influenced by skeletal muscle mass.

The present study enrolled 130 patients with T2D (age ≥60; including 11 patients with dementia) and excluded stroke survivors. Their HbA1c levels were recorded every ≤12 weeks for >5 years. All patients underwent VF tests. We analyzed the correlation between VF z-scores (standardized total scores) and glycemic control values (time-weighted average and maximum HbA1c levels for the past 5 years), or disease durations. As controls, we also investigated the relationships between stages of diabetic retinopathy (NDR/NPDR/PDR) and past glycemic controls. The mean patient age was 74.7 years, the mean HbA1c at the baseline was 7.5%, median duration of education was 12 years, and mean disease duration was 18.3 years. Significant correlates for VF z-scores were age, years of education, and dementia in addition to glycemic control values. VF z-scores tended to correlate with average HbA1c levels, and significantly correlated with maximum HbA1c levels for the past 5 years. The relationships between VF z-scores and maximum HbA1c levels remained significant after adjusting for age, years of education, and dementia. Generally, VF z-scores were strongly associated with maximum HbA1c levels for longer observation periods, i.e., VF z-scores correlated with maximum HbA1c levels for the past 5 years, best compared with maximum HbA1c levels for the past 4 years. As controls, diabetic retinopathy stages were also associated with average and maximum HbA1c levels. The diabetes duration was associated with diabetic retinopathy stages strongly, but not with VF z-scores. These results suggest that executive dysfunction may be caused by metabolic mechanisms other than diabetic retinopathy.
Epidemiology—Aging

History of Falls in the Previous Year Predicts Frailty among Community-Dwelling Older Patients with Diabetes Mellitus

Willy MARCOS VALENCIA, NIMA MOGHADAM, JAVIER BALDA-CANIZARES, MICHAEL J. MINTZER, STUTI DANG, JORGE G. RUÍZ, Miami, FL

Frailty is a state of vulnerability to stressors resulting in higher morbidity, mortality and healthcare utilization in older adults. Diabetes mellitus is considered a risk factor for both frailty and falls in older adults. The aim of this study was to determine in a community cohort of older patients (65 years and older) with type 2 diabetes mellitus (T2DM) whether a history of falls is associated with frailty. Community dwelling older Veterans with T2DM underwent frailty assessment with the validated 5-item FRAIL Scale (frail ≥ 3; pre-frail 1-2; robust 0 point) between January 2016 and December 2017. We aggregated data on patients with at least one fall in the previous year. Binomial logistic regression was used to examine the association between a history of falls in the previous year and frailty. Among 886 patients (mean age 74 ± 7.9 years; 58% men; 31% robust, 36% prefrail, and 33% frail), 565 experienced at least one fall in the previous year. In total, 164 falls occurred among 108 older patients. The number of older individuals with at least one fall in the previous year was significantly higher in the frail as compared with prefrail and robust groups: 20%, 9%, and 9% respectively (p<0.0005). A history of falls in the previous year was associated with an increased risk for frailty (odds ratio: 2.54 [95% CI: 1.60–4.03]). The population-attributable risk associated with a history of falls was 44% for frailty.

In conclusion, a history of falls in the previous year is a strong predictor of frailty in older patients with T2DM. Falls should be a key component of the clinical evaluation of older patients with T2DM.

1470-P

Long-Term Effects of Lifestyle Intervention and Metformin during DPP on Appendicular Lean Mass

ANN V. SCHWARTZ, DING PAN, HELEN F. HAZUDA, EDWARD HORTON, MARY A. HOSSINK, RITA R. KALYANI, WILLIAM C. KNOWLER, ANDREAS KRISKA, MATTHIAS SCHLÖGL, HERMES FLOREZ, DPP RESEARCH GROUP, San Francisco, CA, Washington, DC, San Antonio, TX, Brockline, MA, Phoenix, AZ, Baltimore, MD, Pittsburgh, PA, Zürich, Switzerland, Miami, FL, Rockville, MD

Weight loss prevents progression to diabetes but long term effects on lean mass are unknown. We determined if intensive lifestyle modification (ILS), metformin (MET) or placebo (PLB) treatment in the Diabetes Prevention Program (DPP) had differential effects on appendicular lean mass (ALM) and sarcopenic-obesity (SO) ~16 years after DPP randomization in the DPP Outcome Study (DPPOS). During DPP, 3234 participants at high risk for diabetes were randomized to ILS, MET or PLB, 2779 continued in DPPOS and were offered modified group ILS. During DPPOS, ILS was offered additional lifestyle reinforcement semi-annually and MET received unmasked metformin. This analysis includes 1384 DPPOS participants who had dual-energy X-ray absorptiometry hip scans at year 12 (Y12). Osteoporosis was defined as femoral neck BMD T-score ≤ -2.5 and osteopenia as -2.5<T-score<1. Participants were asked at Y12 if they had a fall in the previous year. Outcomes were compared across the 3 treatment groups using Pearson's chi-square tests. Associations between treatment and outcomes were assessed with logistic regression.

Mean age at Y12 was 66.5 (±9.5) years. Mean time since DPP baseline was 15.6 (±0.7) years. Weight loss (DPP baseline to DPPOS Y12) did not differ across treatment groups (-4.4 kg ILS; -3.9 kg MET; -3.1 kg PLB; p=0.14). There were no differences across groups in the prevalence of osteoporosis in men (1.4% ILS, 1.3% MET, 0.7% PLB; p=0.836) or women (2.9% ILS, 2.9% MET, 3.1% PLB; p=0.983). Prevalence of osteopenia was also similar across groups. Prevalence of history of falls was similar across groups in men (18.0% ILS, 16.4% MET, 16.0% PLB; p=0.995) and women (25.7% ILS, 21.3% MET, 21.6% PLB; p=0.342). Prevalence of osteopenia, osteoporosis or history of falls did not differ between ILS or MET and PLB in men or women.

In a cohort at high risk of diabetes, lifestyle intervention or metformin did not have long-term effects on bone density or falls.

Supported By: National Institute of Diabetes and Digestive and Kidney Diseases (U01DK049849)

1471-P

1472-P

Metformin and Lifestyle Interventions in DPP do not Have Long-Term Effects on Bone Density or Falls

ANN V. SCHWARTZ, DING PAN, MANITA ARUDA, JILL P. CRANDALL, ANDREAS KRISKA, CHRISTOPHER S. PROMALLI, MARINELLA TEMPROSA, HERMES FLOREZ, DPP RESEARCH GROUP, San Francisco, CA, Washington, DC, Hyattsville, MD, Bronx, NY, Pittsburgh, PA, Anchorage, AK, Rockville, MD, Miami, FL

Randomization to lifestyle intervention (ILS) or metformin (MET) in the Diabetes Prevention Program (DPP) resulted in weight loss and reduced progression to diabetes. The long term effects of these interventions on bone mineral density (BMD) and falls, both associated with weight loss, are not known. We determined if ILS or MET was associated with prevalence of osteoporosis, osteopenia or history of falls in the DPP Outcome Study (DPPOS).

During DPP, 3234 participants at high risk for diabetes were randomized to ILS, MET or PLB, 2779 continued in DPPOS and were offered modified group ILS. During DPPOS, ILS was offered additional lifestyle reinforcement semi-annually and MET received unmasked metformin. This analysis includes 1384 DPPOS participants who had dual-energy X-ray absorptiometry hip scans at year 12 (Y12). Osteoporosis was defined as femoral neck BMD T-score ≤ -2.5 and osteopenia as -2.5<T-score<1. Participants were asked at Y12 if they had a fall in the previous year. Outcomes were compared across the 3 treatment groups using Pearson's chi-square tests. Associations between treatment and outcomes were assessed with logistic regression.

Mean age at Y12 was 66.5 (±9.5) years. Mean time since DPP baseline was 15.6 (±0.7) years. Weight loss (DPP baseline to DPPOS Y12) did not differ across treatment groups (-4.4 kg ILS; -3.9 kg MET; -3.1 kg PLB; p=0.14). There were no differences across groups in the prevalence of osteoporosis in men (1.4% ILS, 1.3% MET, 0.7% PLB; p=0.836) or women (2.9% ILS, 2.9% MET, 3.1% PLB; p=0.983). Prevalence of osteopenia was also similar across groups. Prevalence of history of falls was similar across groups in men (18.0% ILS, 16.4% MET, 16.0% PLB; p=0.995) and women (25.7% ILS, 21.3% MET, 21.6% PLB; p=0.342). Prevalence of osteopenia, osteoporosis or history of falls did not differ between ILS or MET and PLB in men or women.

In a cohort at high risk of diabetes, lifestyle intervention or metformin did not have long-term effects on bone density or falls.

Supported By: National Institute of Diabetes and Digestive and Kidney Diseases (U01DK049849)

1473-P

Progression of Coronary Artery Calcification Is Associated With Clinically Relevant Cognitive Impairment in Type 1 Diabetes

JINGCHUN GUG, KAREN NUNLEY, CATERINA ROSAND, TREVOR J. ORCHARD, Pittsburgh, PA

An increased risk of cognitive dysfunction has been identified in type 1 diabetes (T1D). The association between cardiovascular disease and dementia has been examined in the general population, but the relationship is not known in T1D. The study assessed the role of coronary artery calcification (CAC) on cognitive impairment in 148 mid-aged T1D patients from the Pittsburgh Epidemiology of Diabetes Complications Study cohort of childhood-onset T1D. Baseline CAC was measured in 1998-99 and repeated 4-8 years later (2000-06). Per extensive neuropsychological testing in 2010-13, 28% (41/148) of participants met the study definition of clinically relevant cognitive impairment (two or more of 7 select test scores ≥1SD below demographically appropriate published norms). Mean age and T1D duration at first CAC measure were 37 and 29 years, respectively. In logistic regression models with backward selection, allowing for previously established risk factors for cognitive impairment in this T1D cohort (sex, T1D duration, BMI, HbA1c, ApoE4 status, ankle-brachial index, statin use, proliferative retinopathy, distal symmetric polyneuropathy, and QDI), initial CAC volume was associated with cognitive impairment (OR: 1.08, 95% CI: 1.02-1.15; p=0.023). Those with an initial CAC-0 (n=68), including both CAC volume and density scores in the model along with other risk factors, both CAC volume (positively OR: 1.21 (1.07-1.37)) and CAC density (inversely OR: 0.41 (0.18-0.89)) were associated with cognitive impairment. In those with repeated CAC...
measures (n=116), the annual progression of CAC volume (determined by Hokanson method) doubled the odds of having cognitive impairment (OR: 1.96 (1.18-3.28)).

Progression of CAC volume was independently associated with clinically relevant cognitive impairment in mid-age adults with long lasting T1D. In those with prevalent CAC, CAC density appears to protect against cognitive impairment when controlling for CAC volume.

Supported By: National Institutes of Health

EPIDEMIOLOGY—AGING

1474-P
Life-Course Glucose Trajectory and Cognitive Function in Middle Age—Evidence from the Bogalusa Heart Study
PATRICK STUCHLIK, OWEN CAMERICH, EMILY HARVILLE, HUA HE, MARYLEN ROMERO, JEANETTE GUSTAT, VIVIAN FONSECA, LYDIA A. BAZZANO, New Orleans, LA, Baton Rouge, LA

Although the adverse effects of elevated glucose on cognitive function have been well-documented, most cognitive evidence comes from older adults. In this study, we make use of repeated measurements across five decades of the Bogalusa Heart Study and latent class methodology to examine the association of glucose from childhood through early adulthood on cognitive function in middle age. From our cohort of n=1,296 adults, after adjustment for age, sex, race, BMI, diabetic status, smoking, physical activity, and depressive symptoms, we identified four trajectory classes of glucose over the life course: (1) “healthy and stable,” (2) “healthy but slightly increasing,” (3) “decreasing,” and (4) “sharply increasing” (Figure). The distributions of trajectory class membership were modeled with a relative cognitive z-score, computed from a battery of tests covering major neuropsychological domains. Mean z-scores, where higher indicates better relative cognitive function, for classes 1-4 were 1.04, 0.85, 0.19, and -6.69, respectively. Parameter estimates were positive for classes 1-3, and negative for class 4 (p<0.05). The “sharply increasing” class was inversely associated with each individual cognitive test except Logical Memory II-Recognition. Our findings suggest increasing glucose trajectories may adversely affect cognition earlier in adulthood than previously thought.

Figure.

Glucose Trajectory Classes

1475-P
Joint Associations of Diabetes and Sarcopenia on All-Cause Mortality among U.S. Older Adults
JIN XIA, YIQING SONG, Indianapolis, IN

Background: Recent studies have shown that sarcopenia defined as the loss of muscle mass and/or strength was associated with diabetes and independently predicted all-cause mortality in older adults; however, it is unclear whether sarcopenia and diabetes synergistically affect all-cause mortality.

Methods: We aimed to prospectively examine joint associations of sarcopenia (defined by either low muscle mass (LMM), low muscle strength (LMS), or both) and diabetes on all-cause mortality in a nationally representative sample of U.S. adults, including 4,449 participants aged 50 years and older from NHANES 1999-2002 with linked mortality data. Weighted multivariable logistic regression models were adjusted for age, sex, race, BMI, smoking, alcohol use, education, leisure time physical activity, sedentary time, and comorbid diseases.

Results: Overall, we had 971 with diabetes and 921 with sarcopenia defined by both LMM (ALM/BLM) and LMS. The prevalence of sarcopenia was higher in diabetic than non-diabetic individuals (23.7% vs. 14.6% for LMM, 15.8% vs. 13.8% for LMS, and 4.0% vs. 3.5% for both LMM and LMS). In the joint analyses, diabetic individuals had increased risk of all-cause mortality than those without diabetes or LMM, whether they had LMM (OR=2.79, 95% CI: 1.56-4.98) or not (OR=1.40, 95% CI: 1.02-1.92) (P for joint effect=0.001). LMS was associated with higher risk of all-cause mortality among both diabetic (OR=4.10, 95% CI: 1.59-10.55) and nondiabetic individuals (OR=2.39, 95% CI: 1.77-3.23) (P for joint effect=0.011). Compared to those without diabetes or sarcopenia (both LMM and LMS), all-cause mortality risk was higher among individuals with sarcopenia alone (OR=1.78, 95% CI: 1.15-2.75) (P for joint effect=0.011).

Conclusions: Our results suggest that LMS was independently and strongly associated with elevated risk of all-cause mortality, with additional risk synergistically with diabetes among U.S. older adults.

1476-P
Secular Trend for Cancer Incidence in Type 2 Diabetic Patients and the Association between Type 2 Diabetic Patients and Cancer between 2004 and 2014
JINGLUO, HUIN XIU, ONG, Shanghai, China

Background: Type 2 diabetes mellitus (T2DM) has been suggested to increase the risk of cancers. The aim of this study was to evaluate the secular trend for cancer incidence in T2DM patients in Minhang District of Shanghai and the incidence rate ratios from cancer between T2DM patients and the general population between 2004 and 2014.

Methods: All T2DM patients were enrolled from the standardized management system based on local electronic information system in Minhang District of Shanghai, China. Newly-diagnosed cancer cases were identified by record-linkage with the Shanghai Cancer Registry. The incidence rates (per 100,000) from cancer according to age for the T2DM patients for each year between 2004 and 2014 were calculated. Age-specific incidence from cancer for T2DM patients and their Standardized incidence ratios (SIR) and 95% confidence interval (CI) compared with the general population were estimated.

Results: A total of 2,593 T2DM patients (1,317 male and 1,276 female) aged ≥40 years were included. A trend for an increase in the annual rate was observed for all age groups. The incidence (per 100,000) from cancer was 597.17 in male and 829.57 in female, with age-standardized rate (ASR) being 207.12 and 218.57, respectively. Parameter estimates were positive for classes 1-3, and negative for class 4 (p<0.05). The “sharply increasing” class was inversely associated with each individual cognitive test except Logical Memory II-Recognition. Our findings suggest increasing glucose trajectories may adversely affect cognitive function in middle age. From our cohort of n=1,296 adults, after adjustment for age, sex, race, BMI, diabetic status, smoking, physical activity, and depressive symptoms, we identified four trajectory classes of glucose over the life course: (1) “healthy and stable,” (2) “healthy but slightly increasing,” (3) “decreasing,” and (4) “sharply increasing” (Figure). The distributions of trajectory class membership were modeled with a relative cognitive z-score, computed from a battery of tests covering major neuropsychological domains. Mean z-scores, where higher indicates better relative cognitive function, for classes 1-4 were 1.04, 0.85, 0.19, and -6.69, respectively. Parameter estimates were positive for classes 1-3, and negative for class 4 (p<0.05). The “sharply increasing” class was inversely associated with each individual cognitive test except Logical Memory II-Recognition. Our findings suggest increasing glucose trajectories may adversely affect cognition earlier in adulthood than previously thought.

Figure.

Glucose Trajectory Classes

1477-P
Trajectories of Health-Related Quality of Life (HR-QoL) in Older Adults with Diabetes
SUNHEE PARK, TAEWHA LEE, Seoul, Republic of Korea

Background: Health-related quality of life (HR-QoL)—a major outcome of diabetes management interventions—is a general self-rated concept regarding one’s biological functions, symptoms, and functional status. However, there is limited information on the longitudinal changes in HR-QoL of older adults over time.

Objective: To identify different patterns of HR-QoL changes in longitudinal data and reveal potential predictors of these trajectories among older adults with diabetes.

Methods: Subjects were older adults over 65 years with diabetes (n = 440), who participated in the Korea Health Panel survey for five consecutive years (2009-2013). HR-QoL, longitudinal data were measured using Euro-Qol 5-Dimension Questionnaire. Growth mixture modeling was used to estimate distinct patterns, and binary and logistic regressions were used to determine factors affecting different trajectories of HR-QoL patterns using STATA 14.0.

Results: Four distinct trajectories of HR-QoL were found to be the best based on the Bayesian information criterion. High decrease HR-QoL indicates constantly high HR-QoL of older adults with diabetes (10.0%) whose HR-QoL remained stable 0.0% whose HR-QoL remained stable (23.7% vs. 14.6% for LMM, 15.8% vs. 13.8% for LMS, and 4.0% vs. 3.5% for both LMM and LMS). In the joint analyses, diabetic individuals had increased risk of all-cause mortality than those without diabetes or LMM, whether they had LMM (OR=2.79, 95% CI: 1.56-4.98) or not (OR=1.40, 95% CI: 1.02-1.92) (P for joint effect=0.001). LMS was associated with higher risk of all-cause mortality among both diabetic (OR=4.10, 95% CI: 1.59-10.55) and nondiabetic individuals (OR=2.39, 95% CI: 1.77-3.23) (P for joint effect=0.011). Compared to those without diabetes or sarcopenia (both LMM and LMS), all-cause mortality risk was higher among individuals with sarcopenia alone (OR=1.78, 95% CI: 1.15-2.75) (P for joint effect=0.011).

Conclusions: Our results suggest that LMS was independently and strongly associated with elevated risk of all-cause mortality, with additional risk synergistically with diabetes among U.S. older adults.

1477-P
Trajectories of Health-Related Quality of Life (HR-QoL) in Older Adults with Diabetes
SUNHEE PARK, TAEWHA LEE, Seoul, Republic of Korea

Background: Health-related quality of life (HR-QoL)—a major outcome of diabetes management interventions—is a general self-rated concept regarding one’s biological functions, symptoms, and functional status. However, there is limited information on the longitudinal changes in HR-QoL of older adults over time.

Objective: To identify different patterns of HR-QoL changes in longitudinal data and reveal potential predictors of these trajectories among older adults with diabetes.

Methods: Subjects were older adults over 65 years with diabetes (n = 440), who participated in the Korea Health Panel survey for five consecutive years (2009-2013). HR-QoL, longitudinal data were measured using Euro-Qol 5-Dimension Questionnaire. Growth mixture modeling was used to estimate distinct patterns, and binary and logistic regressions were used to determine factors affecting different trajectories of HR-QoL patterns using STATA 14.0.

Results: Four distinct trajectories of HR-QoL were found to be the best based on the Bayesian information criterion. High decrease HR-QoL indicates constantly high HR-QoL of older adults with diabetes.
Epidemiology/ Genomics
POSTERS

Epidemiology/ Genetics

Cognitive Impairment and Glycemic Status among U.S. Adults

SARAH CASAGRANDE, CATHERINE C. CÖNVE, SILVER SPRING, MD; BETHESDA, MD

Several studies have shown that cognitive impairment is a complication of diabetes, however, this association has not been assessed in an older, nationally representative U.S. sample. This study determined the association between diabetes and cognitive function overall and by participant characteristics among adults aged ≥60 years in the 2011-2014 National Health and Nutrition Examination Surveys (N=1,552). Participants had diabetes if they reported a physician diagnosis of diabetes, had an A1c ≥6.5%, or fasting plasma glucose ≥126 mg/dL. Cognitive function was assessed by three tests: Consortium to Establish a Registry for Alzheimer’s Disease Word Learning subtest (CERAD W-L), which measures the ability to learn new verbal information; the Animal Fluency test, which measures executive function; and the Digit Symbol Substitution Test (DSST), which measures working memory. The standardized effect size (Cohen’s d: value ≥0.2=small, ≥0.5=moderate, ≥0.8=large) for each cognitive test was determined for those with diabetes vs. those without diabetes. Overall, adults with diabetes performed consistently lower on the cognitive assessments compared to those without diabetes. The overall effect size was moderate for the CERAD W-L and DSST assessments (Cohen’s d range: -0.44 to -0.51), and was small for the Animal Fluency score (Cohen’s d = -0.33) for those with diabetes vs. those without. For the CERAD W-L, the effect size was greatest (∼ -0.50) for youngest ages (60-69 years), non-Hispanic Asians, never smokers, those with normal weight, and no hypertension, compared to counterparts. For the DSST assessment, the effect size was greatest (∼ -0.50) for those age 60-69 years, Mexican Americans, females, former or never smokers, those who did not consume alcohol, those who exercised, those with hyperlipidemia, and those without hypertension.

In conclusion, diabetes was associated with a lower ability to learn new verbal information and poorer working memory but had less of an effect on executive function.

The Burden of Aging with Diabetes and the Impact of Cognitive Decline

BRITTANY L. SMALLS, SHOSHANA H. BARDACH, NANCY SCHONEBERG,LEXINGTON, KY

Objective: T2DM effects approximately 25% of older adults and prevalence of cognitive decline (CD) increases with age. Furthermore, some research suggests that individuals living with these conditions find it difficult to manage their health. The goal of this study was to use the 2015 BRFSS to assess the difference in disease burden experienced by older adults with T2DM and with or without CD.

Research Design and Methods: Older adults with T2DM were assessed for CD based on self-reported affirmative responses to the Cognitive Decline questions. Disease burden was assessed using Healthy Days—Health Related Quality of Life questions. Logistic regression was used to determine the likelihood of disease burden based on cognitive status. Differences in reported days of disease burden between those with and without CD using pairwise comparison of marginal linear predictions. An alpha level of 0.05 was used.

Results: The sample reported an average of 3 chronic conditions in addition to T2DM. Compared to those without CD, those with CD had a 57% increased likelihood of experiencing poor physical health, were 2.7x as likely to report poor mental health, and had a 97% increased likelihood of reporting poor physical or mental health impeded usual activities, including self-care. There was also a significant difference in the number of days of disease burden reported by those with cognitive decline for poor physical (+5.1 days) and mental health (+5.2 days) and the number of days that poor physical or mental health interfered with usual activities (+4.8 days).

Conclusion: As the population ages, it is imperative to understand how CD influences disease burden and ability to perform T2DM-related self-care activities. Future research is needed to understand, along with cognitive decline, how geriatric syndromes and other chronic conditions contribute to disease burden in older adults. Additionally, research is needed to identify potential social determinants that may be unique to older adults with T2DM.
Chronic Sleep Disturbances Are Predictive of Incident Diabetes in Older Adults—Variations by Gender and Race/Ethnicity

HEIDI GUYER, Ann Arbor, MI

Study Objectives: The current study was conducted to determine whether self-reported chronic sleep disturbances are predictive of incident diabetes in older adults, as well as to determine variations by gender and race/ethnicity.

Methods: 7446 participants from the Health and Retirement Study, a nationally-representative longitudinal cohort study of U.S. adults, were followed for eight years, between 2006 and 2014. Chronic sleep disturbance was defined as self-reported trouble falling asleep or staying asleep “most of the time.” Diabetes was based on self-reported doctor’s diagnosis or a Hemoglobin A1C value >6.5 mg/dL. Hazard ratios were calculated for baseline and on-going sleep disturbances.

Results: The average age of participants was 63.5 years. Close to 30% of men and 40% of women reported having a chronic sleep disturbance at baseline. The cumulative incidence of diabetes was 17.7% among men and 15.2% among women. Both men and women who developed diabetes were more likely to report chronic sleep disturbances at baseline than those who did not develop diabetes (men: 32.2% vs. 27.3%; women: 44.2% vs. 36.0%). Women were more likely to develop diabetes within eight years than men and women after adjustment for demographic covariates (women: HR 1.40 95% CI: 1.19-1.63; men: HR 1.27 95% CI: 0.98-1.66). Black and Hispanic men and women with chronic sleep disturbances had a greater likelihood of developing diabetes within eight years than white men and women.

Conclusions: Self-reported chronic sleep disturbance is an independent predictor of incident diabetes in women. The likelihood of developing diabetes among those with chronic sleep disturbances is greater for women than men and greater for blacks and Hispanics than non-black/Hispanic older adults. This finding has both public health and clinical relevance in an aging society.

Supported By: National Institute on Aging (U01AG009740)

Increased Cardiovascular Risk in Patients with Diabetes, Statin ‑ Controlled LDL Cholesterol, and Residual Hypertriglyceridemia

GREGORY NICHOLS, SEPHY PHILIP, CRAIG B. GRANOWITZ, KRISTI REYNOLDS, SERGIO FAZIO, Portland, OR, Bedminster, NJ, Pasadena, CA

High triglyceride (TG) levels are common in type 2 diabetes (T2D). We evaluated T2D patients at high risk for CV events who had statin-controlled LDL cholesterol (LDLc) to determine whether the presence of high TG levels contribute to residual CV risk. We combined data from the Southern California and Northwest regions of Kaiser Permanente to identify adults on statin therapy with LDLc 40-100 mg/dL, no other lipid therapies, and with T2D and a prior diagnosis of myocardial infarction, ischemic stroke, peripheral artery disease or at least one other CV risk factor. Patients were grouped into high (200-499 mg/dL, n=5,542) or normal (<150 mg/dL, n=22,411) TGs in 2010 and followed them through December 2016 to compare the adjusted incidence rates and rate ratios of first non ‑ fatal MI, non ‑ fatal stroke, unstable angina, coronary revascularization, death, and their composite. Models were adjusted for demographic and clinical characteristics using generalized linear models with Poisson errors. Over mean follow ‑ up of 5 years, patients with high TG were at increased risk of CV outcomes (Table). High TG levels independently increase CV risk in T2D patients with statin ‑ controlled LDLc. The ongoing CV outcome trial, REDUCE ‑ IT, will determine if high dose pure prescription eicosapentaenoic acid reduces CV risk among statin users with persistently high TG levels, including T2D patients.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Covariates</th>
<th>Rate Ratio ( \pm 95% CI )</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non ‑ Fatal MI</td>
<td>Age, gender, BMI</td>
<td>2.1 (1.8 ‑ 2.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>Non ‑ Fatal Stroke</td>
<td>Age, gender, BMI</td>
<td>1.3 (1.1 ‑ 1.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Unstable Angina</td>
<td>Age, gender, BMI</td>
<td>1.6 (1.3 ‑ 2.0)</td>
<td>0.004</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>Age, gender, BMI</td>
<td>1.2 (1.0 ‑ 1.5)</td>
<td>0.024</td>
</tr>
<tr>
<td>Coronary Revascularization</td>
<td>Age, gender, BMI</td>
<td>1.2 (1.0 ‑ 1.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>All ‑ cause Mortality</td>
<td>Age, gender, BMI</td>
<td>1.1 (1.0 ‑ 1.2)</td>
<td>0.014</td>
</tr>
<tr>
<td>Composite of MI, Stroke, or Death</td>
<td>Age, gender, BMI</td>
<td>1.3 (1.0 ‑ 1.6)</td>
<td>0.020</td>
</tr>
</tbody>
</table>

Supported By: Amarin Pharma Inc.
1487-P
Composite Cardiovascular Risk Factor Target Achievement and Its Indicators in U.S. Adults with Diabetes—The Diabetes Collaborative Registry
NATHAN D. WONG, YANG SONG, SUZANNE V. ARNDT, LAURENCE SPERLING, CHRISTOPHER P. CANNON, SUIXIN INZUCCHI, MIKHAIL KOSIBOROD, INGA, CA, BOSTON, MA, KANSAS CITY, MO, ATLANTA, GA, NEW HAVEN, CT
Background and Objective: Patients with diabetes mellitus (DM) who are at multiple atherosclerotic cardiovascular disease (ASCVD) risk factor (RF) targets have >50% lower ASCVD risks. Limited “real world” data exists on how often such targets are reached. We studied multiple RF target attainment for ASCVD prevention and its indicators in a contemporary DM registry.
Methods: We determined in the U.S. Diabetes Collaborative Registry those at target for HbA1c (<7.0% or <8.0% if with ASCVD), LDL-C (<100 or <70 mg/dl if ASCVD), blood pressure (<130/80 and <140/90 mmHg), and non-smoking status by sex, race, and prior history of ASCVD. Multiple logistic regression examined indicators of target attainment.
Results: In 45,134 persons with DM (mean age 68.7 years, 41% female) the Table shows achievement of RF targets. Age ≥ 65 [odds ratio, OR=2.3] and (inversely) private insurance (OR=0.9), depression (OR=0.8), and multiple DM medications (OR=0.9) (all p<0.05 to p<0.001) were independently associated with being at all 4 targets (including BP<130/80 mmHg). Conclusions: Less than 1 in 6 U.S. adults with DM are achieving comprehensive RF control. Multifactorial interventions will be necessary to optimize the prevention of ASCVD.

1488-P
Impact of Prior Coronary Artery Disease (CAD) and Glucose Tolerance Status (GTS) on Incident CAD in Japanese Men
MASARU KITAZAWA, KAZUYA FUJIHARA, MAYUKO HARADA, MASAHIRO ISHIZAWA, MASHIKO YAMAMOTO, MASANORI KANEKO, TAEKO OSAWA, TAKAHI YABADA, YASUHIRO MATSUBAYASHI, HIROHIITO SONE, NIIGATA, JAPAN
Despite a decade of historical debate and the recent regard regarding diabetes mellitus (DM) as a CAD risk equivalent, few studies have evaluated the impact of prediabetes (preDM) separately. Thus, it is still possible that the impact of DM has been underestimated unless preDM is excluded from the nondiabetic category and independently assessed along with normal glucose tolerance (NGT) and DM. To clarify the independent risk of NGT, preDM and DM with and without prior CAD for incident CAD, we analyzed data using a nationwide claim-based database that included 138,162 men (NGT 78,230; preDM 45,610; DM 14,322) aged 72-78 y in Japan. Multivariate Cox analysis showed that the impact of preDM on CAD was modest compared to DM even with prior CAD (Model 1, Table) whereas prior CAD confers a 5-8-fold excess risk for CAD regardless of GTS (Model 2, Table). The hazard ratio (HR) of CAD in NGT individuals with prior CAD was much higher than in DM individuals without prior CAD (HR 3.08/95% CI: 2.08–4.54). The HR in those with both DM and prior CAD was 16.71/9.18–21.93) compared to NGT without prior CAD.

In conclusion, DM alone is not prior CAD risk equivalent even if the influence of preDM is eliminated. Prior CAD confers a far higher risk for subsequent CAD regardless of GTS. Necessity of intense intervention for the secondary prevention of CAD is implied considering the enormously high risk in those with both DM and prior CAD.

1489-P
The Extent of Severe Periodontal Disease as a Predictor of Cardiovascular Complications and Mortality in Type 1 Diabetes (T1D)
TUMADER KOLHUA, RAHEL G. MILLER, PAULA A. MIORE, TREVOR J ORCHARD, TINA COSTACOU, TINA COSTACOU, TINA COSTACOU, TINA COSTACOU, TINA COSTACOU
This analysis was based on 520 participants (mean age=32.1 years and duration=23.7 years) of the Pittsburgh Epidemiology of Diabetes Complications study of childhood-onset (<17 years) T1D, who during 1992-94 received a comprehensive oral health exam including periodontal assessment of three facial sites (mesial, mid-cervical and distal) of the right maxillary/left mandibular or left maxillary/right mandibular quadrants and who were subsequently followed for up to 19 years to ascertain complication incidence. PD was defined as clinical attachment loss of ≥4 mm for at least 10% of the examined sites. Predictors of all-cause mortality, Hard Coronary Artery Disease (HCAD; CAD death, myocardial infarction or revascularization); and
Conclusions: Foreign-born individuals with diabetes have lower BMI and systolic blood pressure compared to U.S.-born individuals. Prior to adjusting for access to care, foreign-born had higher LDL suggesting the importance of improving access to care and ensuring that CVD risk factors are under control. Interventions focused on lowering LDL among foreign-born individuals will be critical in lowering their cardiovascular disease risk.

1492-P
Comparative Cardiovascular Effectiveness of SGLT2 Inhibitors vs. LiRagilide in Routine Care
ELISABETTA FATTORI, BRENDA M. EVERETT, SEBASTIAN SCHNEEWEBSS, ROBERT J. GLYNN, JUN LIU, SEOYOUNG C. KIM, BOSTON, MA
Both SGLT2 inhibitors (canagliflozin and empagliflozin) and liRagilide have shown cardiovascular (CV) benefits in CV outcome trials. Whether these agents are associated with differential CV effects in routine care remains unexplored. In a large commercial U.S. health insurance database (4/2013-9/2015), we assessed the comparative CV risk of SGLT2 inhibitors (SGLT2) vs. liRagilide in patients with type 2 diabetes. We used 1:1 propensity score (PS) matching to balance over 100 baseline characteristics. We estimated the hazard ratio (HR) of a combined CV outcome (hospitalization for myocardial infarction (MI) or stroke) and heart failure hospitalization (HF). Secondary outcomes included an expanded combined CV outcome (hospitalization for MI, stroke, unstable angina, or coronary revascularization) and individual MI or stroke hospitalization. Over 30 months, SGLT2 initiators had no significant difference in the risk of the combined CV outcome (HR = 0.91 [95% CI 0.76-1.31]) or other secondary CV outcomes, but had an approximatively 30% decrease in the risk of HF (HR = 0.68 [0.50-0.88]), compared with liRagilide (Table). Subgroup analyses in patients with and without baseline CV disease produced largely consistent results.

In conclusion, this study rules out large differences in atherosclerotic CV risk between SGLT2 and liRagilide, but supports larger benefits of SGLT2 vs. liRagilide for HF.

Table. Characteristics and outcomes in 1:1-PS-matched cohort comparing SGLT2 inhibitors vs. liRagilide1

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Both T2D</th>
<th>LiRagilide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Mean (SD)</td>
<td>57.6(13.5)</td>
<td>57.7(13.5)</td>
</tr>
<tr>
<td>Sex (%)</td>
<td>49.8(50.2)</td>
<td>49.2(50.8)</td>
</tr>
<tr>
<td>History of type 2 diabetes (%)</td>
<td>51.7 (53.0)</td>
<td>50.9 (52.2)</td>
</tr>
<tr>
<td>History of acute heart disease (%)</td>
<td>34.9 (36.2)</td>
<td>30.5 (30.8)</td>
</tr>
<tr>
<td>History of lipemic retinopathy (%)</td>
<td>5.3 (5.9)</td>
<td>5.3 (5.9)</td>
</tr>
<tr>
<td>History of congestive heart failure (%)</td>
<td>3.4 (3.9)</td>
<td>3.6 (4.1)</td>
</tr>
<tr>
<td>Diabetes nephropathy (%)</td>
<td>1.4 (1.6)</td>
<td>1.3 (1.6)</td>
</tr>
<tr>
<td>No. antidiabetic medications at index date, Mean (SD)</td>
<td>2.4±1.1</td>
<td>2.3±1.0</td>
</tr>
<tr>
<td>Measured HbA1c at index date, N (%)</td>
<td>7.0±1.9</td>
<td>7.0±1.9</td>
</tr>
<tr>
<td>Level of HDL at index date, N (%)</td>
<td>6.0±2.1</td>
<td>6.0±2.1</td>
</tr>
<tr>
<td>Current smoking status (%)</td>
<td>10.2 (10.5)</td>
<td>9.4 (9.8)</td>
</tr>
<tr>
<td>Combined CV event (hospitalization for MI or stroke)</td>
<td>9.6 (9.8)</td>
<td>9.4 (9.8)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>1.01 (0.76-1.32)</td>
<td>Ref.</td>
</tr>
<tr>
<td>Index hospitalization, N (per 100 person-years)</td>
<td>9.6 (9.8)</td>
<td>10.4 (10.5)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.99 (0.86-1.15)</td>
<td>Ref.</td>
</tr>
<tr>
<td>Expanded combined CV event (hospitalization for MI, stroke, unstable angina, or coronary revascularization), N (per 100 person-years)</td>
<td>105 (14.1)</td>
<td>105 (14.1)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>1.01 (0.80-1.27)</td>
<td>Ref.</td>
</tr>
<tr>
<td>MI hospitalization, N (per 100 person-years)</td>
<td>4.0 (4.7)</td>
<td>4.8 (5.4)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.82 (0.57-1.18)</td>
<td>Ref.</td>
</tr>
<tr>
<td>Stroke hospitalization, N (per 100 person-years)</td>
<td>9.6 (10.3)</td>
<td>10.1 (10.3)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.92 (0.67-1.25)</td>
<td>Ref.</td>
</tr>
</tbody>
</table>

1Follow-up started on the day following treatment initiation and ended at the earliest of a study censoring, treatment discontinuation, treatment withdrawal, or end of study period, whichever came first.

Supported by: National Institute on Aging (K08AG055670 to E.P.)

A1393

1493-P
A Real-World Evaluation of the Association between Cardiovascular Outcomes and T2D Therapy
ELLEN THIEL, WILLIAM D. MARDER, WILLIAM T. CEFALU, MATT PETERSEN, LISA LATTS, Ann Arbor, MI, Cambridge, MA, Arlington, VA, Denver, CO
Data from placebo controlled, randomized clinical trials (RCTs) have demonstrated cardio-protective effects of certain diabetes therapy classes, including sodium-glucose co-transporter-2 inhibitors (SGLT2is), dipeptidyl peptidase-4 inhibitors (DPP-4is) and GLP-1-RAs vs. sulfonylureas (SUs) in a real-world setting. Propensity score weighting and doubly robust methods (boosting and Poisson regression) were used to control for differences in baseline characteristics. The primary study outcomes were hospitalization...
for congestive heart failure, acute myocardial infarction, stroke and a composite of all three. Lower extremity amputations were also examined. The relative risks of events in the 12 months before and after treatment initiation were compared to generate relative risk ratios.

Protective effects of SGLT2is compared to SUis were observed (Table). Interestingly, there was a greater protective effect of DPP-4is on individual outcomes compared to SUis in contrast to DPP-4i vs. placebo in RCTs.

### Table

<table>
<thead>
<tr>
<th>Event</th>
<th>Weighted Risk</th>
<th>Incidence Risk per 1,000 PY</th>
<th>Relative Risk</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>2.58</td>
<td>2.04</td>
<td>1.25</td>
<td>0.002</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>4.13</td>
<td>3.59</td>
<td>1.17</td>
<td>0.099</td>
</tr>
<tr>
<td>Stroke</td>
<td>6.56</td>
<td>5.85</td>
<td>1.11</td>
<td>0.062</td>
</tr>
</tbody>
</table>

### Table 1495-P

**Epigenetic Link between Statin Use and Diabetes**

**CAROLINA OCHOA-ROSALES, ELIANA PORTILLA-FERNANDEZ, RORY WILSON, JANO NANO, MOHSEN GHANBARI, OSCAR L. RUEDA-OCOHA, SR., TERHO LEHTIMAKI, SR., XU GAO, BENJAMIN LEHNE, TRUDY YORDTMAN, OSCAR FRANCO, TAULANT MUKA, SR., Rotterdam, Netherlands, Munich, Germany, Tampa, Finland, Heidelberg, Germany, London, United Kingdom**

Current evidence associates statin use with increased risk of type 2 diabetes (T2D). Mechanism are unclear. Statins may impact DNA methylation, a key regulator in gene expression. We conducted an epigenome-wide association study among 8313 Europeans (7163 never users and 1150 current statin users) from 7 cohorts to assess the association of statin use and DNA methylation in blood. After replication we found genome-wide associations of methylation sites annotated to DHCR24 (cg17901584, cg10177197), SC4MOL (cg05119988), and ABCG1 (cg06500161, cg27243685), which are involved in cholesterol, insulin and lipoprotein lipase pathways. Lower methylation of cg17901584 was associated with higher insulin (P = 0.006). Prevalent T2D was related to all sites except cg27243685 (P from 6 x 10^-10 to 9 x 10^-4). Only cg06500161 independently predicted incident T2D (P = 6 x 10^-7), implicating that ABCG1 may be a causal factor for T2D as suggested by Mendelian Randomization (Figure 1). Our study is the first to provide evidence of DNA methylation as potential mechanism by which statin use can lead to adverse metabolic alterations and subsequently T2D.

Supported By: Chilean Ministry of Education

---

**Epigenetic Link between Statin Use and Diabetes**

**CAROLINA OCHOA-ROSALES, ELIANA PORTILLA-FERNANDEZ, RORY WILSON, JANO NANO, MOHSEN GHANBARI, OSCAR L. RUEDA-OCOHA, SR., TERHO LEHTIMAKI, SR., XU GAO, BENJAMIN LEHNE, TRUDY YORDTMAN, OSCAR FRANCO, TAULANT MUKA, SR., Rotterdam, Netherlands, Munich, Germany, Tampa, Finland, Heidelberg, Germany, London, United Kingdom**

Current evidence associates statin use with increased risk of type 2 diabetes (T2D). Mechanism are unclear. Statins may impact DNA methylation, a key regulator in gene expression. We conducted an epigenome-wide association study among 8313 Europeans (7163 never users and 1150 current statin users) from 7 cohorts to assess the association of statin use and DNA methylation in blood. After replication we found genome-wide associations of methylation sites annotated to DHCR24 (cg17901584, cg10177197), SC4MOL (cg05119988), and ABCG1 (cg06500161, cg27243685), which are involved in cholesterol, insulin and lipoprotein lipase pathways. Lower methylation of cg17901584 was associated with higher insulin (P = 0.006). Prevalent T2D was related to all sites except cg27243685 (P from 6 x 10^-10 to 9 x 10^-4). Only cg06500161 independently predicted incident T2D (P = 6 x 10^-7), implicating that ABCG1 may be a causal factor for T2D as suggested by Mendelian Randomization (Figure 1). Our study is the first to provide evidence of DNA methylation as potential mechanism by which statin use can lead to adverse metabolic alterations and subsequently T2D.

Supported By: Chilean Ministry of Education

---

**Statin therapy**

**Table 1495-P**

<table>
<thead>
<tr>
<th>Event</th>
<th>Weighted Risk</th>
<th>Incidence Risk per 1,000 PY</th>
<th>Relative Risk</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>2.58</td>
<td>2.04</td>
<td>1.25</td>
<td>0.002</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>4.13</td>
<td>3.59</td>
<td>1.17</td>
<td>0.099</td>
</tr>
<tr>
<td>Stroke</td>
<td>6.56</td>
<td>5.85</td>
<td>1.11</td>
<td>0.062</td>
</tr>
</tbody>
</table>

### Table 1494-P

**Epicatechin Modulates Vasoreactivity and Mitochondrial Function in Endothelium**

**AMY C. KELLER, SARA E. HULL, LESLIE KNAUB, ASPEN JOHNSTON, JANE E. REUSCH, Aurora, CO, Tucson, AZ, Denver, CO**

Vascular dysfunction heralds the onset of diabetic cardiovascular disease. We have reported that vascular mitochondrial dysfunction contributes to impaired vasoreactivity in diabetes. The botanical compound (-)-epicatechin (EPICAT) is a known vasodilator. We hypothesized that EPICAT restores vasodilation by bolstering mitochondrial function in the context of high glucose via support of endothelial nitric oxide synthase (eNOS) activity and mitigation of reactive oxygen species (ROS). To test this hypothesis, we examined the impact of EPICAT on vasoreactivity ex vivo and endothelial cell function in vitro. EPICAT significantly increased endothelium dependent acetylcholine-stimulated vasodilation (64.74%, p=0.002). HUVEC cells were incubated with 7 mM (normal glucose, NG) or 30 mM glucose (HG) with or without 0.1 µM EPICAT for 30 min, 2, 4-6 hours, and 24 hours. Mitochondrial superoxide was detected via electron spin resonance spectroscopy, and respiration and hydrogen peroxide were measured using Oroboros. Mitochondrial superoxide production was elevated in HG cells (2 hours=1.63 ± 0.17 µM/mg (HG) vs. 1.18 ± 0.07 µM/mg (NG), p=0.017 and 4-6 hours=1.46 ± 0.16 µM/mg (HG) vs. 1.18 ± 0.07 µM/mg (NG), p=0.09). Mitochondrial respiration was greater in cells exposed to HG for 2 hours in state 3 (23.8%) and uncoupled (14.5%), and hydrogen peroxide was higher in HG treated cells, while both metrics were unchanged after 6 hours, and respiration was decreased after 24 hours. Cells pretreated with EPICAT had elevated rates of respiration (state 3=73.4% and uncoupled=55.2%) without a commensurate increase in superoxide, and EPICAT dampened HG superoxide generation after 2 hours by 17.0%. Cells pretreated with EPICAT and exposed to HG had significantly elevated eNOS protein expression (p=0.001). Our data suggest that EPICAT potentiates vasodilation by acutely activating eNOS, leading to an increase in mitochondrial respiration while mitigating excess ROS production.

Supported By: U.S. Department of Veterans Affairs, National Institutes of Health; Nutrition Obesity Research Center
Pericardial Adipose Tissue and Coronary Calcium in Type 1 Diabetes—The CACTI Study

AMENA KESHAWARZ, LAURA PYLE, AMY C. ALMAN, CAPRICE SASSANO, ELIZABETH WESTELDT, RACHEL M. SIPL, JANET K. SNELL-BERGEON, Aurora, CO;ampa, FL.

Type 1 diabetes (T1D) and menopause are associated with higher risk of coronary artery calcium (CAC). Accumulation of pericardial adipose tissue (PAT), a pro-inflammatory visceral fat higher in post-menopausal women and associated with increased CAC, may be a mechanism by which T1D is associated with higher CAC risk. We examined the effect of PAT on the relationship between T1D and CAC in women over time. PAT and CAC volume data were collected from CT heart scans over 4 study visits from 725 women enrolled in the Coronary Artery Calcification in Type 1 Diabetes (CACI) study (mean baseline age ± SD 37 ± 3 years). We used repeated measures modeling to examine changes in square root-transformed CAC volume over time by T1D, menopausal status, and quartile of PAT volume after adjusting for age, central obesity, and study visit. PAT levels did not differ by T1D status (33.5 vs. 33.7, p=0.8), but there was a significant interaction between PAT, menopause, and T1D (p=0.02) in relation to CAC volume (Figure 1). In T1D women, higher PAT was associated with higher CAC volume regardless of menopause status, but the effect was greater in post-menopausal women. There was no difference in CAC in non-diabetic (non-DM) women across PAT quartiles or by menopause status. CAC was higher in T1D than non-DM women regardless of menopause status and PAT quartile. PAT has a greater effect on CAC in women with T1D than non-DM women despite similar PAT volumes.

Incidence and Risk of Celiac Disease in Individuals with Type 1 Diabetes over the Lifespan—A Population-Based Cohort Study Using the Health Improvement Network Database

MARY ELLEN VAJRAVITO, DIVA DE LEON, DAVID R. WEBER, RON KEREN, MICHELLE R. DEGENBURG, RITU VERMA, ROCHESTER, NY.

Objective: Individuals with type 1 diabetes (T1D) are at increased risk for celiac disease (CD), though the incidence for those diagnosed with T1D beyond childhood is unknown. We used survival analysis to investigate the incidence and risk factors for diagnosis of CD over time in a population-based cohort of children and adults with T1D.

Methods: Retrospective cohort study using the Health Improvement Network (THIN), a primary care electronic medical records database of >13 million people in the United Kingdom. Subjects were 1-35 years old at T1D diagnosis; subjects with type 2 diabetes or prevalent CD were excluded. We used Cox proportional hazards regression to identify factors associated with diagnosis of CD during follow-up. Risk factors assessed included age at T1D, sex, year of T1D diagnosis, and time-varying covariates of thyroid disease and adrenal insufficiency.

Results: Subjects (n=11,537; 43% female) had a median follow-up time of 6.8 years (IQR 2.5-14.1). CD was diagnosed in 234 (2%), with median time to diagnosis of 2.9 years (IQR 1.2-7.8); 37% were diagnosed > 5 years after T1D. Incidence (per 10,000 person-years) was greater in females than males (26.9 [95% CI 22.4-31.9] vs. 16.4 [95% CI 13.4-19.9]) and in subjects <10 years at diagnosis of 2.9 years (IQR 1.2-7.8); 37% were diagnosed > 5 years after T1D. Incidence (per 10,000 person-years) was greater in females than males (26.9 [95% CI 22.4-31.9] vs. 16.4 [95% CI 13.4-19.9]) and in subjects <10 years at T1D diagnosis (50.1 [95% CI 41.4-60.2] vs. 13.3 [95% CI 11.0-15.9]). In multivariable Cox regression, the hazard of CD was higher with younger age (HR 0.88 per year of age at T1D diagnosis, 95% CI 0.80-0.96, p=0.006), in females (HR 1.50, 95% CI 1.16-1.94, p=0.002), and with more recent year of diagnosis (HR 1.09, 95% CI 0.97-1.12, p<0.001).

Conclusions: A significant proportion of CD cases were diagnosed more than 5 years after T1D diagnosis, the time frame currently recommended for screening. A more personalized approach to CD screening, accounting for the greater risk for younger-onset and female patients with T1D, may be warranted to minimize over-testing while limiting missed diagnoses.

Screening Patients for Diabetes in a Large, National Clinical Database

NKRITA STEMPELNICK, JOHN K. CUDDERBACK, CORI R. RATTELMAN, ELIZABETH L. CLEMMING, Alexandria, VA.

Objective: To characterize diabetes screening patterns among eligible patients per ADA Standards of Medical Care in Diabetes using a large, geographically diverse clinical database.

Study Design: Retrospective descriptive analysis conducted in a clinical database containing over 25 million patient records. Population Studied: A total of 5.1 million patients aged 18-75 in 23 health care organizations (HCOs) with at least one outpatient visit in the study period (7/2016-6/2017), no prior diagnosis of diabetes mellitus, and no prior diabetes medication prescriptions (except metformin).

Principal Findings: Among 5.1 million patients, 74% were eligible for screening and 55% were screened according to guidelines. Adequate screening ranged from 47%-76% across 23 HCOs. Adults 65 and older were most likely to be adequately screened (61%, P < .01). Least likely to be screened were patients with low-income insurance types (P < .01); non-
One-Hour Oral Glucose Tolerance Tests (OGTTs) for the Prediction and Diagnostic Surveillance of Type 1 Diabetes (T1D)
KIMBER SIMMONS, JAY SOSENKO, HEBA M. ISMAIL, HELENA ELÖNG LARSSON, ANDREA STECK, Aurora, CO, Miami, FL, Pittsburgh, PA, Malmö, Sweden

Natural history studies and prevention trials for T1D use 2 hour OGTTs for two main goals: prediction and diagnostic surveillance. Although 2 hour OGTTs are reliable for these purposes, they impose time burdens and costs for research participants and staff. We thus examined whether 1 hour OGTTs are suitable for prediction and diagnostic surveillance. To assess their accuracy for prediction, we developed a 1 hour risk score similar to the Diabetes Prevention Trial-Type 1 Risk Score (DPTRS). The DPTRS utilizes log fasting C-peptide, sum of 30, 60, 90 and 120-min glucose and C-peptide, age, and log BMI. The components are the same for the 1 hour risk score (DPTRS60) and the DPTRS except that 1 hour glucose and C-peptide replace the glucose sum and C-peptide sum. Diabetes Prevention Trial-Type 1 participants were included in the analysis (n=670; age at baseline: 13.8±9.6 years; 56% male; 241 diagnosed with T1D). 1 hour glucose and C-peptide were highly predictive of T1D within the DPTRS model, as were log fasting C-peptide, age, and log BMI (all p<0.001). The receiver operating characteristic AUC was almost identical for the DPTRS and DPTRS60 (both 0.81, p<0.001). To assess diagnostic accuracy, we sought to identify a 1 hour glucose threshold below which a diagnosis of T1D would be unlikely. Of 162 (among the 241 total) diagnosed by 2 hour OGTTs, only 2 (1.2%) had a 1 hour glucose <180 mg/dl at diagnosis. Of 172 with a 1 hour glucose <180 mg/dl at baseline who were ultimately diagnosed, only 1 (0.6%) was diagnosed before the 6.3 month window for the next monitoring visit. 568/670 (85%) had a 1 hour glucose <180 mg/dl at baseline. These findings show that 1 hour OGTTs are virtually as predictive of T1D as 2 hour OGTTs. Also, it appears that a 1 hour glucose <180 mg/dl ensures a very low risk for T1D before the next routine monitoring visit. Moreover, most 1 hour glucose values are <180 mg/dl. Accordingly, 1 hour OGTTs can reduce time burdens and costs for the major- ity of T1D natural history and prevention trial participants.

Supported By: American Diabetes Association (1-14-CO-17) to A.S.J., JDFR

Higher HbA1c Levels Should Be Used to Diagnose Diabetes and Prediabetes in Blacks
LISA R. STAIMEZ, CHRISTOPHER N. FORD, LAUREN DANIELS, ADRIANA GONZALEZ-ZARAI, FARAH N. KHAN, MARY RHEE, PETER W. WILSON, LAWRENCE S. PHILLIPS, Atlanta, GA, Decatur, GA

Blacks have higher HbA1c levels than whites with similar glucose levels, suggesting that universal diagnostic criteria could lead to overdiagnosis of diabetes and prediabetes in blacks. We hypothesized alternative HbA1c diagnostic criteria could reduce misclassification in blacks. Data from 3,603 non-Hispanic (NH) white (67.6%) and 1,721 NH black (32.4%), nonpregnant adults (18-70 year) were included from 5 cycles (2005-2014) of the National Health and Nutrition Examination Survey with HbA1c and plasma glucose measures (i.e., fasting and 2 hour from oral glucose tolerance test. OGTT). Diabetes and prediabetes by HbA1c was compared with ‘true’ OGTT classification to identify alternative HbA1c values with the lowest misclassification (false positives + false negatives). Survey-weighted rates were computed across a set of HbA1c cutoffpoints for diabetes (HbA1c ≥6.5% to ≥7.3%) and HbA1c ranges for prediabetes (4.9-5.5% to 6.8-7.5%) in 0.1% increments. By ADA OGTT criteria, the prevalence of diabetes and prediabetes in whites was 4.6% and 42.1%, respectively, and in blacks, 4.2% and 36.9%. Under ADA criteria for diabetes, misclassification was similar in whites (3.7%) and blacks (3.5%), but blacks had 6.3 times the rate of false positives (1.1% blacks vs. 0.2%, p<0.001) and 0.76 times false negatives (57.3 vs. 75.1%, p=0.016). Diabetes misclassification was lowest in whites at HbA1c ≥6.3% (3.4% misclassified) and in blacks ≥6.9% (3.2%). Prediabetes misclassification was similar in whites (35.8%) and blacks (23.5%), but blacks had 2.6 times the rate of false positives (24.5% vs. 9.8%, p<0.001) and 0.68 times that of whites (50.0 vs. 73.2%, p<0.001). Misclassification was lowest in whites at HbA1c 6.6-6.3% (34.3% misclassified) and in blacks at 5.9-6.6% (31.3%).

Conclusion: Overdiagnosis of diabetes and prediabetes is disproportionately high among NH blacks compared to NH whites. Increasing the HbA1c diagnostic thresholds by 0.3-0.6% for NH blacks could potentially avert 3.2 million false positive diagnoses.

Supported By: National Institutes of Health (U1TR002798)

Clinical and Socioeconomic Characteristics Associated with Ketoadosis at Diagnosis of Type 1 Diabetes in Italian Children—Nationwide Survey, 2014-2016
VALENTINO CHERUBINI, RICCARDO BONIFANTI, EDILMA SRRAM, LUCIA FERRITO, ROSARIA GESUITA, STUDY GROUP FOR DKA IN ITALY, Ancona, Italy, Milan, Italy

To analyse clinical and socioeconomic factors associated with diabetic ketoacidosis (DKA) at diagnosis of type 1 diabetes (T1D) in Italy. Incident cases less than 15 years of age, were recruited during 2014-2016 from 31 paediatric centres. Age, gender, presence of coeliac or thyroid disease, HbA1c, minority status, residence, family history of T1D and parents’ level of education were collected. DKA was defined according to ISPAD criteria. Point and 95% CI of DKA frequency were estimated. Two logistic regressions were performed to evaluate the role of clinical and socioeconomic characteristics on the risk of overall and severe DKA, considered as present vs. absent. A total of 1430 cases were evaluated. Severe and mild DKA frequencies were of 12.4% (95% CI: 10.8-14.3%) and 26.4% (95% CI: 24.1-28.7%), respectively. Females, minority status and younger children were at significant higher risk of DKA. Family history of T1D and high mater- nal education were significantly associated with a lower risk. Despite preven- tion campaigns intended to reduce the DKA recently implemented, the frequency of DKA at T1D diagnosis remains high in Italy. Multiple factors affect the risk of DKA at the onset of type 1 diabetes, suggesting potential opportunity to intervene between symptom onset and development of dia- betic ketoacidosis for both parents and clinicians.

Table. Factors Associated with the Risk of DKA at Diagnosis of Type 1 Diabetes in Italy.

<table>
<thead>
<tr>
<th>Age class</th>
<th>OR 95% CI</th>
<th>p</th>
<th>OR 95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-9 yrs</td>
<td>0.66</td>
<td>0.45-0.97</td>
<td>0.03</td>
<td>0.48</td>
</tr>
<tr>
<td>10-14 yrs</td>
<td>0.68</td>
<td>0.47-1.00</td>
<td>0.09</td>
<td>0.42</td>
</tr>
</tbody>
</table>

| Gender | Males vs. females | 0.73 | 0.54-0.98 | 0.03 | 0.68 | 0.41-1.05 | 0.086 |

| Mother’s level of education | 0.76 | 0.60-0.95 | 0.07 | 0.59 | 0.42-0.83 | 0.003 |

| Family history | No vs. Yes | 0.43 | 0.22-0.79 | 0.09 | 0.36 | 0.11-0.92 | 0.006 |

| Minority status | No vs. Yes | 2.05 | 1.29-3.27 | 0.002 | 1.29 | 0.60-2.60 | 0.498 |

With the diabetes epidemic spreading across Africa, undiagnosed diabe- tes threatens health. As the reproducibility of the OGTT in Africans is not known, the value of using the OGTT to diagnose diabetes (DM) in Africans is uncertain. Therefore, the Africans in America study enrolled 62 blacks (71% male, age 40±11y (mean±SD), BMI 27.8±4.6 kg/m2) who were born in Africa, identified as healthy and currently living in the Washington, DC area. Two OGTT were performed with 11±9 days between tests. The OGTT was used to define normal glucose tolerance (NPT), prediabetes (preDM) and DM. For reproducibility, the k statistic was used and interpreted by conven- tional standards (slight 0.00 to 0.20, fair 0.21 to 0.40; substantial 0.61
to 0.80, excellent 0.81 to 1.0). At the 1st OGTT, NGT, preDM and DM were diagnosed in 40%, 26% and 34% of Africans, resp. At the 2nd OGTT, NGT, preDM and DM were diagnosed in 40%, 32% and 27%. Sensitivity of A1C + GA was similar to A1C alone (P = 0.13). For the non-GA and the combined tests were: 67%, 29% and 79% resp. (Figure A). In the Africans were: 43% vs. 35%, P = 0.20, resp. In the OB, sensitivities of A1C, GA and the combined tests were: 62% resp. (Figure B). Sensitivity increased when the tests were combined because abnl-GT was detected in 22 nonobese Africans not identified by A1C alone. 

Addition, some cross-sectional studies have suggested that adiponectin may play a role in PreD development. Therefore, there are still few prospective cohort studies, which could successfully demonstrate a causative relationship between adiponectin and PreD. The aim of this study was to establish the significance of Adipo (serum total adiponectin level) as a biomarker for PreD in Japanese workers. To this end, we analyzed data in our prospective occupational-based cohort study, which has been conducted since 2008. A total of 551 workers without PreD aged 20-60 years were followed-up (mean follow-up period 4.2 years). The subjects were divided into four categories based on the quartiles of baseline Adipo for each sex (male: < 4.9, 4.9-6.6, 6.7-8.9 and > 8.9 µg/ml, female: < 8.2, 8.2-11.1, 11.2-13.9 and > 13.9 µg/ml). The age- and sex-adjusted incidence of PreD significantly increased with decreasing quartile of Adipo at baseline (P for trend < 0.001). In multivariate analyses after adjusting for age, sex, BMI, smoking habit, alcohol intake, regular exercise, HDL cholesterol, triglycerides, family history of diabetes, and hypertension, the hazard ratio of PreD was 1.64 [95% confidence interval: 1.08 to 2.51, P = 0.02] in the second quartile and 1.33 [95% confidence interval: 0.83 to 2.11, P = 0.24] in the lowest quartile, when compared with the highest quartile. Furthermore, the risk of PreD was 5% higher (P = 0.04) with a per 1 µg/ml decrement of Adipo in the multivariate-adjusted model. These results suggest that decreased Adipo is a risk factor for the incidence of PreD in Japanese workers, which could assign a new role to Adipo as a biomarker for the early stage of glucose homeostasis disorders, besides being a biomarker for the development of diabetes and cardiovascular events.

Supported By: Japan Society for the Promotion of Science; Japan Society for the promotion of Science, Education, Culture, Sports, Science and Technology; Tokushima Prefecture; Otsuka Pharmaceutical Co., Ltd.

**EPIDEMIOLOGY—CLINICAL—DIAGNOSIS AND SCREENING**

**Combining A1C with Glycated Albumin Improves Detection of Abnormal Glucose Tolerance in Nonobese Africans—The Africans in America Study**

JEAN DAMASCENE KABAKAMIRA, SARA M. BRIKER, RAFEAL L. BAKER, JR., CHRISTOPHER DUBOSE, LILIAN MABUNDO, STEPHANIE T. CHUNG, DAVID E. SACKS, ANNE E. SUMNER, Bethesda, MD

As diabetes prevalence rises in Africa, tests to detect abnormal glucose tolerance (abnl-GT) must be optimized. Recent reports suggest A1C performs well as a diagnostic test for abnl-GT in the OB. In contrast, glycated albumin (GA) contributes to the detection of abnl-GT in the nonobese. To determine if BMI affects sensitivity of A1C and GA in Africans, we evaluated the sensitivity of A1C and GA separately and combined to detect abnl-GT in 88 OB blacks (age 42 ± 10 y, BMI 33.4 ± 2.9, range 30.0-42.4) and 232 nonobese blacks (age 38 ± 10 y, BMI 25.5 ± 2.6, range 18.2-29.8) who were born in Africa and live in the U.S.A. Abnl-GT was determined by glucose criteria for the OGTT. Thresholds for A1C and GA were defined by the cut-off at their upper quartile (A1C ≥ 5.7%; GA ≥ 13.97%). Prevalence of abnl-GT in OB and nonobese Africans were: 43% vs. 35%, P = 0.20, resp. In the OB, sensitivities of A1C, GA and the combined tests were: 67%, 29% and 79% resp. (Figure A). In the OB, sensitivity of A1C + GA was similar to A1C alone (P = 0.13). For the nonobese, sensitivities of A1C, GA and the combined tests were: 35%, 38% and 62% resp. (Figure B). Sensitivity increased when the tests were combined because abnl-GT was detected in 22 nonobese Africans not identified by A1C alone. Patterns were similar by sex and region of Africa. Data from Africans living in the U.S.A suggest detection of abnl-GT in the nonobese is improved by combining A1C with GA.

**WITHDRAWN**

**Serum Total Adiponectin Level Is Associated with Incident Prediabetes in Japanese Workers**

AKIKO HATA, MASASHI MIYOSHI, TAKAYUKI NAKAO, TAKAKO ICHIHARA, AYAKO TANUMA, TAKAKO MINAGAWA, YUMI KUWAMURA, MAKOTO FUNAKI, Tokushima, Japan, Takamatsu, Japan

Emerging evidence suggests that adiponectin secreted into the serum by adipocytes may be involved in the development of type 2 diabetes. In addition, some cross-sectional studies have suggested that adiponectin may be related to PreD (prediabetes). Thus, it is reasonable to expect that adiponectin may play a role in PreD development.
Lower Hepatic Insulin Sensitivity in a Family with a Recently Described Glucokinase Gene Variant

KÁLMÁN BÓDIS, DANÁ P. ZAHARIA, VÁNISLAVA KARUSHEVA, PAVEL BOBOV, DANIEL F. MARKGRAF, BIRGIT KNEBEL, YULIYA KUPIRYANOVA, JONG-HEE HWANG, VOLKER BURKART, KARSTEN MÜSSIG, MICHAEL ROEDEN, JULIA SZNIDER, Düsseldorf Germany

Mutations in the gene encoding glucokinase (GCK) cause maturity-onset diabetes of the young (MODY 2). Characterized by impaired prandial insulin secretion and hepatic glycogen storage. Recently diagnosed patients with type 1 diabetes (T1D) exhibit impairment of both beta cell function and hepatic energy metabolism. Thus, this study aimed at examining the effect of MODY 2 on hepatic insulin sensitivity and energy metabolism. Carriers of one recently described GCK mutation (D124N; c.370; GAC>AAC in exon 4) were compared to controls (CON) with similar sex, age and body mass index (BMI) (female/male: 1.2 vs. 3.5; 35.4 vs. 35.2 years; 20.1±1.8 vs. 25.7±1.5 kg/m²) from the German Diabetes Study (Registration, Clinicaltrials.gov NCT01409330). Whole body and hepatic insulin sensitivity (IS) were assessed by Botnia-clamp tests with [6,6-²H₂]glucose. Beta cell function was determined from incremental AUC(C-peptide)₀⁻⁶₀/[AUCglucagon]₀⁻⁶₀ during intravenous glucose tolerance test. Hepatocellular lipid content (HCL), γATP and inorganic phosphate (Pi) were measured with ¹H/³¹P magnetic resonance spectroscopy. MODY 2 patients had higher hemoglobin A1c (0.6±0.1 vs. 5.2±0.1%, p<0.001) along with approximately 62% lower glucose-stimulated C-peptide secretion than CON (p<0.05). They also had lower hepatic IS (1.8±0.1 vs. 2.3±0.1 mg/(kg*min), p<0.05), but similar whole body IS (12.6±1.9 vs. 13.1±1.5 mg/(kg*min), p=0.87) compared to CON. However, HCL (1.0±0.9 vs. 0.5±0.2%, p=0.48), γATP (3.5±0.3 vs. 3.5±0.6 mmol/l, p=0.99) and Pi (1.9±0.5 vs. 2.9±0.7 mmol/l, p=0.45) in the liver were comparable between both groups.

In conclusion, these data show that lower hepatic IS, but not abnormal hepatic energy metabolism, underlies the previously reported reduction in prandial hepatic glycogen synthesis. Moreover, impairment of hepatic IS is not necessarily associated with hepatic mitochondrial function.

Supported By: German Ministry of Culture and Science of the State of North Rhine-Westphalia; German Federal Ministry of Health; German Federal Ministry of Education and Research

Hypertension Is Associated with a Higher Progression Rate of Insulin Resistance and the Incidence of Diabetes

CHIA-HUNG LIN, HUNG-YUAN LI, Taipei, Taiwan

Background: Hypertension is a risk factor of diabetes. However, the underlying mechanisms are not fully elucidated. Therefore, we investigated this issue in a prospective cohort in Taiwan.

Methods: A total of 1177 subjects without diabetes at baseline were enrolled from 2006 to 2016 at National Taiwan University Hospital Yun-Lin branch with a median follow-up period of 4.5 years. Diabetes was diagnosed by the results of OGTT and HbA1c, or if antidiabetic agents were used. Insulin resistance index by the Homeostatic model assessment 2 (HOMA2-IR) were used to estimate insulin resistance.

Results: Subjects with hypertension by the JNC7 criteria had higher HOMA-IR at baseline and was associated with increased incidence of diabetes, adjusted for HOMA2-IR and BMI, HbA1c, plasma triglyceride, age, gender, family history of diabetes and plasma CRP (adjusted HR 1.51, 95% CI 1.04-2.20, p=0.030). Subjects with treated hypertension had the highest risk of diabetes, followed by subjects with newly-diagnosed hypertension, compared with subjects with pre-hypertension and normal subjects. The progression rate of HOMA2-IR every 5 years (ΔHOMA2-IR/5 year) was higher in subjects with hypertension than in subjects without hypertension (adjusted p<0.001). Subjects with treated hypertension had the highest ΔHOMA2-IR/5 year, followed by subjects with newly-diagnosed hypertension, compared with normal subjects (adjusted p for trend<0.05). However, hypertension by the 2017 ACC/AHA criteria was not significantly associated with incident diabetes in adjusted models. The ΔHOMA2-IR/5 year for hypertension by this criteria was lower than that by the JNC7 criteria.

Conclusion: Hypertension is associated with an accelerated progression of insulin resistance and an increased risk of diabetes. Application of 2017 ACC/AHA criteria for hypertension attenuates the associations.
The Role of NT-proBNP as a Biomarker in Evaluating Residual Cardiovascular Risk in 200 Type 2 DM Patients Optimized for Conventional CV Risk Markers over Two Years

VISHAL GUPTA, VAISHALI TELI, Mumbai, India

Methodology: Two hundred T2DM patients who were on standard glucose lowering agents and who may be on lipid and blood pressure lowering agents were optimised for conventional CV risk markers and followed up for a period of 2 years. We evaluated CV risk using markers like BMI, HbA1c, Systolic blood pressure (SBP), diastolic BP (DBP), total cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides (TG), non-HDL cholesterol, cholesterol remnant, highly sensitive CRP (hsCRP), serum creatinine, eGFR and urine microalbumin/creatinine ratio (UACR). At the end of 2 years, N-terminal pro-b type natriuretic peptide (NTpro-BNP) was measured to assess its role as a residual CV risk marker. T2DM patients with recent history (<1 years) of revascularization or any major surgery were excluded. Data was analysed using SPSS version 20 and represented as Mean ± 2SD with 95% confidence interval, paired t test was used and p value of 0.05 was considered significant.

Results: Baseline characteristics were: 101(50.5%) males and 99 (49.5%) females, mean age was 61.63 ± 9.84 years, mean age since diagnosis 11.89 ± 7.3y and mean BMI 30.53 ± 5.7 kg/m². There was an overall significant reduction from baseline to 2 years in HbA1c (7.61 ± 1.7 to 6.8 ± 1.05; p<0.001), TC (142.55 ± 42.79 to 134.88 ± 40.56, p<0.001), LDL (79.79 ± 35.98 to 70.37 ± 30.69, p<0.001), TG (142.55 ± 42.79 to 134.88 ± 40.56, p<0.001), LDL (79.79 ± 35.98 to 70.37 ± 30.69, p<0.001), HDL (47.86 ± 11.79 to 50.96 ± 14.01, p<0.001). Serum creatinine, eGFR and urine microalbumin/creatinine ratio (UACR). At the end of 2 years, N-terminal pro-b type natriuretic peptide (NTpro-BNP) was measured to assess its role as a residual CV risk marker. T2DM patients with recent history (<1 years) of revascularization or any major surgery were excluded. Data was analysed using SPSS version 20 and represented as Mean ± 2SD with 95% confidence interval, paired t test was used and p value of 0.05 was considered significant.

Conclusion: In the present study, in spite of reduction in various CV risk markers over a period of 2 years, mean NTpro-BNP level remained high. Hence, this may suggest the role of NT pro BNP to be of additional value as a CV risk assessment tool in T2DM patients.
The Prevalence of Undiagnosed Diabetes Has Not Decreased in Spite of Increased Screening in an Australian Rural Area

DAVID SIMMONDS, KRISTEN BLESTER, JUANNA, J. MAGLIANI, SIAN J. WRIGHT, LISA BOURKE, Campbelltown, Australia; Wangaratta, Australia; Melbourne, Australia; Shepparton, Australia

In the mid-2000s in Australia, national guidelines were introduced to promote diabetes screening in people aged 40+ years. We have tested whether diabetes screening has increased, and the prevalence of undiagnosed diabetes has decreased since the introduction of these guidelines. ‘Crossroads’ is a repeat cross-sectional study conducted between 2000-2003 (Crossroads-I) and then 2016-2018 (Crossroads-II) in rural Australia (the Goulburn Valley, Victoria). Households visited were randomly selected, and the same households were then revisited in Crossroads-II, alongside proportionately randomly selected new houses. All adult residents are interviewed face to face by trained research assistants. Questions enquire about diabetes status, occurrence of diabetes screening in last 2 years and primary care utilisation. Randomly selected participants are invited to attend a ‘clinic’ including a glucose tolerance test. The Crossroads-I cohort (n=3787) was younger and had a higher proportion of male participants than the Crossroads-II cohort (n=1733) (44 ± 17% vs. 53 ± 19% p<0.0001, 46% vs. 42% male, p<0.0001). The age standardised prevalence of self-reported diabetes (7.0% vs. 5.4%, p<0.05), and age standardised screening rates (56.5% vs. 49.7%, p<0.05) were higher in Crossroads-II than Crossroads-I. Crude undiagnosed diabetes prevalence was also higher in Crossroads-II than Crossroads-I (77/430 (3.9%) vs. 15/814 (1.8%) p<0.05). Primary care utilisation was higher in Crossroads-II than in Crossroads-I (1.6 vs. 4.7 visits in past 12 months, p<0.0001) and waiting times were shorter (3.0 vs. 3.9 days, p<0.0001). We conclude that diabetes screening has increased in line with the overall prevalence of diabetes. Additional strategies are required to reduce undiagnosed diabetes rates further.

Supported By: National Health and Medical Research Council of Australia

---

Evaluation of FINDRISC with Latin American Abdominal Perimeter

MOSKOWITZ, JAMES H. ANDERSON, JR., AMY MECHLEY, CARRIE J. SZABLOWSKI, EMILY SUSCHA, KADDY DAVIS, CHARLES Z. XIE, KEITH MOSKOWITZ, JAMES H. ANDERSON, JR., AMY MECHLEY, Indianapolis, IN

Introduction: Diabetes screening questionnaires such as FINDRISC need to be evaluated in the target population taking into account their own characteristics.

Material and Methods: A cross-sectional study of diagnostic tests was carried out. We found Original FINDRISC (OF) and Modified FINDRISC (MF) scores with Latin American abdominal obesity cut-offs (male ≥ 94 cm and female ≥ 80 cm) to determine dysglycemia including impaired fasting glucose (IFT), glucose intolerance (GIT), and diabetes mellitus (DM), according to Oral Glucose Tolerance Test in workers of the Maria Auxiliadora Hospital. The Area under the ROC Curve (AURC) of the MF and OF was found. The sensitivity, specificity, positive likelihood ratio (PLR) and negative likelihood ratio (NLR) of each MF and OF point were calculated. A PLR>2 was rated as useful and one greater than 10 as excellent, and an NLR<0.1 was considered useful and <0.1 as excellent.

Results: OF 549 subjects, 77.5% were female, 70% were 45-years old, 75% had a BMI> 25 and 85.4% abdominal obesity with Latin American criteria. About 15% had some history of hypertension or diabetes. MF presented greater accuracy than OF (AUROC: 0.71 vs. 0.69, p = 0.007). There were no differences in the curves between women and men. The score 11 obtained a sensitivity and specificity of 78.8% and 53.0% respectively and the score 14 a sensitivity and specificity of 56.1% and 76.7% respectively. A PLR of 14 is rated useful and an excellent 21. On the other hand, one NLR qualifies a score of 11 as useful and 2 as excellent.

Conclusion: MF had greater diagnostic accuracy than OF for dysglycemia. Scores of 14 and 21 confer high and very high risk; on the contrary, scores of 11 and 2, low and very low risk.

To Evaluate Patient Characteristics in Those with Elevated NT-proBNP in Type 2 DM Patients Optimized for Conventional CV Risk Factors—Card Care for Two Years

VISHAL GUPTA, VAISHALI TELI, Mumbai, India

Methodology: Two hundred T2DM patients on standard glucose lowering agents and who are on lipid and blood pressure lowering agents were followed up for 2 years for improvement in CV risk markers like BMI, HbA1c, systolic blood pressure (SBP), diastolic BP (DBP), total cholesterol (TC), HDL, non-HDL, LDL, triglycerides (TG), cholesterol remnant (CR), highly-sensitive CRP(hsCRP), serum creatinine (Cr) and eGFR. T2DM patients with recent history of revascularisation or any major surgery were excluded. At the end of 2 years, NT-proBNP was measured as an assessment tool for residual CV risk. Those with higher NT-proBNP >125 were identified and patient level characteristics as described above were analysed and compared to patients with NT-proBNP <125. Data was analysed using SPSS version 20, represented as Mean ± 2SD[37] with 95% CI, descriptive statistics and independent t test was used and p value of less than 0.05 was considered statistically significant (Sp). Results: Baseline characteristics of patients with elevated NT-proBNP were: 40(45.05%) males and 34 (45.95%) females, mean age 63.5 ± 10.61 years, mean age since diagnosis 13.5 ± 7.3 years and mean BMI 29.4 ± 5.32 kg/m². The mean values at the end of 2 years in patients with elevated NT-proBNP were: HbA1c 6.7 ± 1.3, SBP 132 ± 24, DBP 72 ± 179, TC 174 ± 2.14, LDL 70.57 ± 3.92, TG 131 ± 31.9, HDL 38.8 ± 13.02, non-HDL 90.18 ± 37.44, CR 23.11 ± 17.7, Cr 1.01 ± 0.29, eGFR 79.29 ± 25.2, hsCRP 140.22 ± 48.98, LDL 90.18 ± 37.44, CR 23.11 ± 17.7, Cr 1.01 ± 0.29, eGFR 79.29 ± 25.2, hsCRP 140.22 ± 48.98. There was an increase in the area in association with improved access to primary care, and guideline changes. Despite this, rates of undiagnosed diabetes have also increased in line with the overall prevalence of diabetes. Additional strategies are required to reduce undiagnosed diabetes rates further.

Supported By: National Health and Medical Research Council of Australia

---

Diabetes Screening Questionnaires—Diagnosis

GABRIEL J. SZABLOWSKI, EMILY SUSCHA, KADDY DAVIS, CHARLES Z. XIE, KEITH MOSKOWITZ, JAMES H. ANDERSON, JR., AMY MECHLEY, Indianapolis, IN

Background: Hemoglobin A1C (A1C) is routinely used to screen, diagnose, and monitor diabetes. A1C is the desired tool to assess glycemic status as it reflects 90 days of glycemic control and does not require fasting. Point-of-care (POC) A1C offers rapid turnaround enabling direct patient engagement. POC A1C tests are indicated for monitoring, but not screening or diagnosis, due to perceived inaccuracy and imprecision. To counter this impression, we evaluated the performance of two POC A1C analyzers relative to the clinical laboratory (CL).

Method: Blood from 48 subjects was collected with A1C values from 4.8-12.0% A1C. Capillary blood was analyzed on the PTS Diagnostics A1CNow® system and Siemens DCA Vantage® while venous blood was tested at external labs on the Tosoh GS and Roche Cobas® c1113 as CL comparators. For reference, venous blood was analyzed on the Roche Cobas Integra® 400 plus. Regression analysis was used to evaluate accuracy and paired differences to measure bias. Clinical risk was calculated using A1C category cut points of <5, 7, 5-7.6-4, and ≥ 8.5% A1C. Chi-squared test was used to assess differences between methods. Precision was performed on the POC systems using 10 replicates at approx. 4.5, 7, and 10% A1C.

Results: Average paired biases were identical for the POC and CL analyzers (-0.04% A1C). Slopes were 0.97, 0.99, and 0.97 for the A1CNow+, DCA, and CL analyzers (p = 0.71) and intercepts were 0.15, 0.04, and 0.12 (p = 0.99). Regression values were 0.987, 0.996, and 0.998, respectively. Clinical risk agreement was 94% for A1CNow+, 99% for the DCA, and 98% for CL analyzers (p = 0.17). Pooled precision was 3.3% CV for A1CNow+ and 1.7% CV for DCA.

Conclusion: The A1CNow+ and DCA were shown to be as accurate as the clinical lab in measuring A1C values. Risk analysis showed no statistical differences between the CL and POC analyzers in classifying diabetes. The A1CNow+ and DCA are valuable tools in evaluating the diabetic state and provide physicians with real-time information to better care for patients.

---

Conclusion: Patients with elevated NT-proBNP were older, had greater D-BP, TC, LDL, TG, non HDL, CR, Cr and weight and lower HDL and eGFR compared to patients without elevated NT pro BNP at 2 year.
1519-P
Circulating Metabolites and the Risk of Type 2 Diabetes—A Prospective Study of 10,938 Young Adults from Four Finnish Cohorts
ARI V. AHOLA-OLLI, LINDA MUSTEELIN, MARIA KALIMI, JOHANNES KETTUNEN, JARI J. JOKELAINEN, JUHA AUVINEN, KATRI S. PUUKKA, AKI S. HAVU-LINNA, TONI KURHMAA, SI. MIKA KÄHÖNEN, VESKO SALOMAA, MARKUS PEROLA, MARJU-RIITTA JARVELIN, MIKA ALA-KORPELA, PETER WURTZ, Turku, Finland, Helsinki, Finland, Oulu, Finland, Tampere, Finland, London, United Kingdom, Melbourne, Australia
Background: Advances in metabolomics have allowed high-throughput metabolic profiling of large population samples. We aimed to identify circulating lipids and metabolites predictive of the risk for type 2 diabetes in young adults.
Methods: Nuclear magnetic resonance metabolomics was used to quantify 229 metabolic measures in 10,938 individuals from four Finnish cohorts (mean age 35 years, range 24-45). Associations between baseline metabolites and diabetes onset during 7-15 years of follow-up (330 incident cases) were assessed by logistic regression adjusted for sex, baseline age and glucose.
Findings: Out of 229 metabolic measures, 174 were associated with risk for incident diabetes in meta-analysis of the four cohorts (P<0.01), range of odds ratios (OR) per 1-SD: 0.41-1.85). Among the strongest biomarkers were increased concentrations of branched-chain and aromatic amino acids (OR: 1.54-1.74) and triglycerides in very-low-density lipoproteins (VLDL; OR: 1.78), and lower levels of omega-6 fatty acids (OR: 0.61) and free cholesterol within large high-density lipoprotein (HDL; OR: 0.41). A biomarker score was derived in three of the cohorts, comprised of phenylalanine, free cholesterol in large HDL, and the ratio of cholesterol esters to total lipids in large VLDL. When validated in the fourth cohort, those in the upper quartile of the biomarker score had considerably higher 15-year-risk for diabetes compared to those in the lowest quartile (OR: 1.61).
Interpretation: Metabolic aberrations across multiple molecular pathways are predictive of the long-term risk of type 2 diabetes in young adults. Comprehensive metabolic profiling may facilitate targeting preventive interventions at young asymptomatic individuals at increased risk for type 2 diabetes.

1520-P
Impact of Patient-Centered Factors on Comparative Effectiveness of Initial Therapies in Treatment-Naive T2D
MARCO A. TESTA, ALEXANDER TURCHIN, MAXWELL SU, DONALD C. SIMONSON, BOSTON MA
The 2017 ADA and AACE consensus statements recommend individualizing A1C targets based on patient-centered demographic, clinical, and socio-economic factors, and also starting initial therapy with metformin. We used benchmarking algorithms to predict personalized A1C outcomes and stratify individuals based on predicted A1C targets. Logistic regression and survival models for achieving target A1C were used for 1:3 matched cases on age, sex, and baseline A1C values. A1C was compared between obesity and diabetes states.
Findings: Of 229 metabolic measures, 174 were associated with risk for incident diabetes in meta-analysis of the four cohorts (P<0.01), range of odds ratios (OR) per 1-SD: 0.41-1.85). Among the strongest biomarkers were increased concentrations of branched-chain and aromatic amino acids (OR: 1.54-1.74) and triglycerides in very-low-density lipoproteins (VLDL; OR: 1.78), and lower levels of omega-6 fatty acids (OR: 0.61) and free cholesterol within large high-density lipoprotein (HDL; OR: 0.41). A biomarker score was derived in three of the cohorts, comprised of phenylalanine, free cholesterol in large HDL, and the ratio of cholesterol esters to total lipids in large VLDL. When validated in the fourth cohort, those in the upper quartile of the biomarker score had considerably higher 15-year-risk for diabetes compared to those in the lowest quartile (OR: 1.61).
Interpretation: Metabolic aberrations across multiple molecular pathways are predictive of the long-term risk of type 2 diabetes in young adults. Comprehensive metabolic profiling may facilitate targeting preventive interventions at young asymptomatic individuals at increased risk for type 2 diabetes.

1521-P
Continuous Glucose Monitoring in Youth with Pre-Type 1 Obesity/Pre-Type 2 Diabetes and Cystic Fibrosis
CHRISTINE L. CHAN, ANDREA STECK, TIM M. VIGERS, LAURA PYLE, FRAN DONG, JESSICA THURSTON, MARIAN REWERS, PHIL ZEITLER, KRISTEN J. NADEAU, ANDREW COON
Continuous glucose monitoring abnormalities are present in the prediabetic state, but how these abnormalities compare among individuals at risk for different types of diabetes (type 1, type 2, vs. cystic fibrosis related diabetes) is unknown. We compared CGM patterns of three distinct groups of youth at risk for diabetes, all with A1c >5.5%; pre-T1D (multiple islet antibody positive), obese/pre-T2D (BMI ≥85%ile), and cystic fibrosis (CF). None were on insulin or other medications affecting glucose metabolism. CGM was obtained for 3-7 days in our observational studies. Pre-T1D youth (A1C range 5.0-6.3%) were randomly matched 1:3 on A1c to the obese/pre-T2D and CF youth. Groups were compared using random effects models for continuous variables. Age, Sex distribution and HbA1c were not different between the groups after matching. The results are shown in the Table. Of interest, youth with CF and pre-T1D had greater standard deviation, higher maximum and lower minimum glucose levels than obese/pre-T2D youth.
In conclusion, CGM patterns are significantly different in pre-T1D and CF compared to obese/pre-T2D, reflecting differences in pathophysiology among these disease states. Early insulin deficiency appears to manifest as greater glycemic variability—higher SD, greater peaks and lows—in pre-T1D and CF, while insulin resistance leads to increased, but less variable, glucose levels in obese/pre-T2D youth.

Table.

<table>
<thead>
<tr>
<th>CGM measure (sensor glucose)</th>
<th>Pre-T1D</th>
<th>Pre-T2D</th>
<th>CF</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average glucose (mg/dl)</td>
<td>117 (3)</td>
<td>114 (2)</td>
<td>111 (2)</td>
<td>0.17</td>
</tr>
<tr>
<td>Standard deviation (SD)</td>
<td>26 (2)</td>
<td>16 (1)</td>
<td>22 (1)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Minimum</td>
<td>62 (4)</td>
<td>77 (2)</td>
<td>62 (2)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>% time &lt;120</td>
<td>37 (5)</td>
<td>31 (4)</td>
<td>27 (2)</td>
<td>0.24</td>
</tr>
<tr>
<td>% time &gt;120</td>
<td>17 (4)</td>
<td>12 (3)</td>
<td>9 (1)</td>
<td>0.23</td>
</tr>
<tr>
<td>% time &gt;200</td>
<td>1.3 (0.7)</td>
<td>0.4 (0.2)</td>
<td>0.8 (0.2)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

*Pre-T1D and CF significantly different from pre-T2D.

Supported By: National Institutes of Health; Cystic Fibrosis Foundation Therapecs Inc.
in older and younger subjects. However, for both age groups the sensitivity of the HbA1c criterion is poor in this patient population.

1523-P
Using MetS Severity to Track Risk for T2D during Intervention with Lifestyle and Metformin
MARK D. DEBEREE, STEPHANIE L. FLUPF, MATTHEW J. GURKA, Charlotteville, VA, Gainesville, FL.
While a metabolic syndrome severity Z-score (MetS-Z) predicts incident type 2 diabetes (T2D) in observational cohorts, it is unclear whether MetS-Z can track response to medical intervention and whether changes in MetS-Z during treatment reflect altered risk for T2D. We evaluated data from the Diabetes Prevention Program, which randomized individuals with glucose intolerance (age 51±11 years) to receive: placebo (n=882), metformin 850 mg bid (n=867), or an intensive lifestyle modification program (n=827). We assessed levels of MetS-Z and the individual MetS components during 3 years of intervention (figure), revealing 1-year decreases in MetS-Z among those treated with lifestyle (effect size -0.6), metformin (-0.3) and placebo (-0.1), driven by improvements in the individual MetS components. We assessed how change in MetS-Z affected T2D risk, finding that each 1-point increase in a participant’s effect size of MetS-Z between 0 and 1 year (difference per participant/baseline SD) increased odds of incident T2D by year 3 by 70% (adjusting for intervention group; Figure). This positive association was found in individual models and in a joint model that included changes in MetS-Z and in each MetS component—suggesting independent associations of changes in MetS-Z with future T2D risk. These data support MetS-Z as an important outcome to follow for response to medical treatment in research studies and clinical care.

Figure.

In conclusion, there is an excess burden of cardio-metabolic disease on uninsured adult Latinos in Santa Barbara. Supported By: Cottage Health; Towbes Foundation; Crawford Idema Family Foundation

1525-P
Estimation of Population Insulin Sensitivity (SI) from Sparsely Sampled Oral Glucose Tolerance Test (OGTT) Data
DARKO STEFANOVSKI, GUILLERMO E. UMPIERREZ, PRIYATHAMA VELLANKI, Philadelphia, PA, Atlanta, GA.
The oral glucose tolerance test (OGTT) minimal model analysis by Cobelli et al. obtains estimates of insulin sensitivity (SI) based on mathematical models that are highly concordant with the euglycemic clamp, the gold standard for estimation SI. This model requires a minimum of 7 blood samples during the 2-hour OGTT. However, in many OGTT studies, the number of samples is below the number that permits the estimation of SI. One way to address (overcome) this issue is by pooling sparsely sampled data (<7 samples) from a specific cohort to obtain population estimates of parameters of S_i. Here we present a novel methodology of estimating population SI using sparsely-sampled OGTT protocol. A cohort of 8 African American subjects (3 Female/5 Male) without a known history of T2D underwent 76-gm OGTTs with 8 samples performed at 0, 15, 30, 60, 90 and 120 minutes. The population SI was estimated concurrently fitting the data from all subjects. We obtained population estimates of SI using from 3 to 6 samples per subject. SI estimates for each subject were also calculated. Sparse-sampling population estimated S_i varied from S_i=4.7±3.0 10^{-4} (mu/l) min^{-1} for 3 samples to S_i=6.4±2.4 10^{-4} (mu/l) min^{-1} for 3 samples. The individual estimates of S_i had a mean of S_i=4.7±2.4 10^{-4} (mu/l) min^{-1}. S_i obtained with the sparse-sampling methodology did not differ from the mean individual estimates of S_i. We conclude that Sparse-sampling estimation of S_i (<3 samples) is a useful tool for estimation of population parameters of SI where there are not enough observations per subject to estimate individual insulin sensitivity. This methodology will provide better phenomenating of insulin sensitivity for studies where previously more crude measures were used. Supported By: HD085850, DA0930381

1526-P
Performance of Clinical/Proteomic Biomarker Panels to Predict Coronary Artery Disease Presence or Cardiovascular Prognosis in Patients With and Without Diabetes Mellitus
SHREYA SHRESTHA, DAI P. MCCARTHY, NASRIEN E. IBRAHIM, ROLAND VAN KIMMENADE, HANNA GAADIN, RENATA MUKAI, CRAIG A. MAGARET, GRADY BARNES, RHONDA F. RHYNE, JAMES JANUZZI, JR., Boston, MA, Nijmegen, Netherlands, Kirkland, WA.
Background: Patients with diabetes mellitus (DM) are at increased risk for prevalent coronary artery disease (CAD) and incident major adverse cardiac events (MACE) such as cardiovascular death, myocardial infarction, and stroke. Prediction of risk in those with DM may be challenging. Using unbiased proteomics we recently described biomarker panels to predict prevalent CAD (HART-CAD) and incident MACE (HART-CVE; both Prevencio, Kirkland, WA) in unselected patients undergoing diagnostic cardiographic angiography. In this study, we sought to compare accuracy of these panels in patients with and without DM.

Methods: The HART-CAD panel includes 2 clinical variables (male sex and prior PCI) and 4 biomarkers: adiponectin, apolipoprotein CIII, kidney injury molecule 1 (KIM 1), and midkine. The HART-CVE panel includes 4 biomarkers: amino-terminal pro-B type natriuretic peptide, KIM 1, osteopontin, and tissue inhibitor of matrix metalloproteinase-1. These panels were derived in 167 DM and 482 non-DM patients; performance of each was validated in a second cohort of patients (N=278) with and without DM.

Results: In patients with DM, the HART-CAD panel had excellent performance for prediction of coronary stenosis >70%, with area under the curve (AUC) of 0.81 (p<0.001), sensitivity 85%, specificity 69%, and positive predictive value (PPV) 58% for detection of CAD, results comparable to those without DM. HART-CVE was highly predictive of incident 1 year MACE in those with DM: AUC of 0.80 (p=0.002), sensitivity 78%, specificity 69%, PPV 47%, and NPV of 90%, again, comparable to those without DM. In Kaplan-Meier analyses, an elevated HART-CVE score predicted shorter time to first MACE (p<0.001).

Conclusion: Previously described cardiovascular biomarker panels effectively predict prevalent CAD and risk for incident MACE in at-risk patients with DM. Supported By: Prevencio, Inc.
A Novel Ceruloplasmin Mutation Causing Aceruloplasminemia with Diabetes in China

YUANYUAN XIAO, Shanghai, China

Background: Hereditary aceruloplasminemia is a rare adult-onset autosomal recessive disease characterized by a ceruloplasmin (CP) gene mutation and defective or absent ceruloplasmin function. The absence of ceruloplasmin leads to pathological iron overload in the liver, pancreas, retina, and central nervous system. It is clinically characterized by diabetes mellitus, anemia, retinal degeneration and neurological abnormalities.

Material and Methods: A 34-year-old Chinese woman who had had diabetes mellitus characterized by fast plasma glucose increasing for more than 3 years. She had tried all kinds of hypoglycemic medicines, the postprandial blood glucose could be well controlled, but still had a fast hyperglycemia. Here, we reported the identification, clinical characterization, and analysis of a novel mutation in the ceruloplasmin gene of this patient and her family members.

Results: Laboratory findings revealed a complete undetectable serum Cp. Increased serum ferritin levels, elevated iron saturation, as well as results of iron quantification in the liver and CT scan also suggested iron overload in the liver. Imaging examination showed a pronounced hyperintensity in the bilateral putamina, caudate, thalamus and dentate nuclei suggesting the presence of iron overload. By sequencing the ceruloplasmin gene, a novel homozygous ceruloplasmin gene mutation, c.146+10T, was identified as the cause of aceruloplasminemia in this patient. Another healthy family members were heterozygous as well.

Conclusion: So far, less than 60 families cases of aceruloplasminemia have been reported world-wide and mainly missense and nonsense mutations in the ceruloplasmin gene were detected. There was only one case about aceruloplasminemia has been reported in China before. We report herein a case of aceruloplasminemia accompanied by diabetes with a novel mutation of CP gene, which suggests that increased awareness should be paid to this disorder as diabetes is an important typical symptoms of it.

Supported By: National Natural Science Foundation of China

A Novel Maturity-Onset Diabetes of the Young (MODY) in a Racially Diverse Pediatric Population

SHILPI RELAN, FRANCES C. HESSEL, KELLY D. TIMMONS, RONA SONABEND, MARIA J. REDUDIO, Houston, TX

Current practice guidelines recommend considering a diagnosis of MODY in patients with a strong family history but without typical features of type 2 diabetes (T2D) [i.e., obesity, insulin resistance, high-risk ethnicity] or type 1 diabetes (T1D) [i.e., islet autoantibodies].

We aimed to test if these criteria apply to a racially diverse pediatric patient population.

Using EPIC Population Health, we retrospectively reviewed electronic medical records (IRB H-41512) of youth diagnosed with MODY between 2013-2017 in a large academic pediatric hospital in Southwestern U.S.

We found that, out of 46 patients with MODY, 50% (n=23) had MODY 2, 17.3% (n=8) MODY 3, 17.5% (n=8) MODY 5, 8.6% (n=4) MODY 1, 2.1% (n=1) MODY 4, and 8.6% of patients had a clinical diagnosis of MODY due to inability to perform molecular testing. The mean (SD, range) age of diabetes diagnosis was 10.1 years (4.4, 2-17); 52% of patients were females; 50% were non-Hispanic white, 32.5% Hispanic, 6.5% African American, 2.2% Asian and 2.2% others/unknown. Notably, 15.2% (n=7, all with a molecular diagnosis of MODY) had positive islet antibodies, 8.6% (n=4) Hashimoto’s thyroiditis and 2.1% (n=1) vitiligo. Obesity/overweight was present in 23.8%, 15.2% had hypertension/prehypertension and 21.7% had dyslipidemia. Diabetes was absent in parents and siblings of 20% (n=12) of patients, although in 5 patients, the mother had gestational diabetes. Persistent microalbuminuria was in 2 youth with MODY 2 and diabetic neuropathy in 1 patient with MODY 2. The mean (SD, range) time between the diagnoses of diabetes and MODY was 14.3 months (22.3, 1-120).

In conclusion, youth with MODY often were of ethnic minorities, lacked a family history of diabetes and had characteristics typical of T1D or T2D, suggesting that the current guidelines to consider a diagnosis of MODY may not apply to a racially diverse U.S. pediatric population. Furthermore, in contrast to previous studies, we identified microvascular complications in youth with MODY 2.
Screening for Cystic Fibrosis-Related Diabetes and Prediabetes—Evaluating 1,5-Anhydroglucitol, Fructosamine, Glycated Albumin, and Hemoglobin A1c

KALIE L. TUMMERDahl, JOHN T. BRINTON, TIM B. VIGERS, KRISTEN J. NADEAU, PHIL ZETTLER, CHRISTINE L. CHAN, Aurora CO, Denver CO

Objective: Dysglycemia in the cystic fibrosis (CF) population is widespread and screening via oral glucose tolerance tests (OGTT) can be burdensome. Our primary aim was to investigate 1,5-anhydroglucitol (1,5AG), fructosamine (Fal), glycated albumin (%GA), and hemoglobin A1c (HbA1c) as screening tests for cystic fibrosis-related prediabetes (CFPD) and cystic fibrosis-related diabetes (CFRD) in youth with CF as defined by the OGTT 2-hour glucose (2hG). Our secondary aim was to determine if alternate screening tests can identify those with better or worse lung function (forced expiratory volume in 1 second, FEV1%; forced vital capacity, FVC%). Youth 10-18 years with CF had 1,5AG, FA, %GA, HbA1c, and a 2-hour OGTT collected during a single study visit. Pearson’s correlation coefficient determined the correlation between all 4 glycemic estimates and 2hG. Receiver Operative Characteristic (ROC) curves were generated. The Youden Index determined optimal cut points for predicting CFPD (2hG≥140-200 mg/dl) and CFRD (2hG≥200 mg/dl). Lung function measures above and below these cutpoints were compared. Fifty-eight youth with CF participated (2hG<140, n=31; CFRD, n=17; CFPD, n=10; mean age 14±3.5 years, 43% male, BMI z-score 0.0±0.8, FEV1% 90±15.0, FVC% 99±14.1, FA, %GA, and HbA1c correlated with 2hG (p<0.05). ROC area under the curve (ROC-AUCs) for all 4 alternate markers were low for both CFPD (0.53-0.67) and CFRD (0.56-0.68). HbA1c had the highest ROC-AUC of 0.68 (95% CI: 0.47-0.84) for identifying CFRD and 0.67 (95% CI: 0.53-0.81) for CFPD. When lung function was compared stratifying above and below the Youden cutpoint for CFRD, only HbA1c identified significant differences in FVC% (105% vs. 96%, p=0.02), FEV1% was not statistically significant (96% vs. 88%, p=0.06). All 4 alternate markers had poor diagnostic accuracy for identifying CFRD by 2hG, although HbA1c may be useful in detecting CFPD and in stratifying individuals with CF by lung function.

Supported By: National Institutes of Health, Cystic Fibrosis Foundation Therapeutics Inc.

Risk of Prediabetes and Diabetes among Those with Impaired Glucose Tolerance: The PREMIER Study

DAVID P. CISTOLA, ALOK K. DWIVEDI, JAMY D. ARD, Winston-Salem, NC

Background: Many studies have reported that diabetes mellitus show the low age tendency. Undiagnosed diabetes patients account for about 25-30% of diabetic patients.

Objective: This study aimed to analyze the epidemiological status and influence factors of prediabetes and diabetes, in order to build screening and intervention system for high-risk population in the primary health care centers.

Methods: A cross-sectional study was conducted. Residents over 35 years old were randomly enrolled from Jun 2016 to Aug 2017 in Electric Heating Hospital (EHH) of Shanghai Minhang District. Data were collected by using questionnaire and physical examination and blood glucose test. Logistic regression was applied to analyze the risk factors for prediabetes and diabetic patients.

Results: A total of 12136 subjects were participated in this screening. Results indicated that 14.54% (n=1765) were diagnosed with diabetes and the prevalence rate in males (17.32%) was significantly higher than in females (12.97%) in each age groups (P<0.001). Furthermore, 20.69% (n=2511) were diagnosed with prediabetes and males were (23.40%) higher than females (19.16%) (P=0.001). Obesity (BMI≥28) (OR=2.35), familial history (OR=1.71), history of cardiovascular disease (OR=1.42), hypertension (OR=1.17), central obesity (OR=1.22), age (OR=1.03), gender (OR=1.3) and sedentary (OR=1.02) were the risk factor for prediabetes or diabetes (p<0.001). In addition, we also found that 54.29% (n=6589) had over 3 risk factors.

Conclusions: It is concluded that we should pay more attention to population with family history and obesity in the screening of diabetes. Gradeing management and screening should be carried out in different stages of diabetes. Comprehensive prevention and control should be taken to slow progress in diabetes.

Are Diabetes Risk Scores the Best Way to Identify Those Who Will Benefit Most from Lifestyle Prevention?

CAROLINA I. SARI, DIANNA J. MAGLIANO, PAUL Z. ZIMMET ESQ., JAAKKO TUUMILEHTO, KUWLLESSR SUHRSSEN, STEPHAN SÖDERBERG, JONATHAN E. SHAW, Melbourne, Australia; Daasam, Kuwait; Fort Louis, Mauritius, Umeå, Sweden

Rationale: Lifestyle intervention programs are effective for preventing diabetes among those with impaired glucose tolerance (IGT), with little evidence of benefit in other high-risk states. The selection of those who are eligible for lifestyle intervention is often made via diabetes prediction tools which identify those at high risk of diabetes. Unless such scores preferentially identify IGT, this will lead to poor performance of diabetes prevention programs. We developed an IGT-specific risk model and a diabetes-specific risk model, and compare their abilities to identify those with IGT.

Methods: Data from population-based surveys conducted in Mauritius in 1992, 1998 and 1998 were used to develop prediction models for IGT and DM. A cross-sectional sample in 1987 was used to develop the IGT model. A cohort sample from 1987 to 1992 was used to develop the DM model. Logistic regression was used to develop the scores. The performances were investigated by calculating area under the receiver operator curve (aROC).

Conclusion: Our results show that risk scores perform poorly in identifying people with IGT, and that without screening identified populations with an oral glucose tolerance test, a high proportion of people entering DM prevention programs will not have IGT—the only state shown to respond to lifestyle.
Circulating Netrin-1 as a Novel Biomarker for Impaired Fasting Glucose and Newly Diagnosed Type 2 Diabetes Mellitus


Aims/Hypothesis: Netrin-1 has been introduced as a neuronal guidance cue acting as a chemotactic and chemorepulsive force during axonal migration. In recent studies, netrin-1 was shown to play various roles including tissue regeneration and modulation of inflammatory activity. Inflammation is one of the major contributing factors in the development of insulin resistance and type 2 diabetes (T2DM). However, little is known about the possible relationship between serum netrin-1 and the risk of T2DM. Therefore, we investigated the association between levels of netrin-1 and glycometabolic parameters.

Methods: Serum samples were collected from a total of 218 individuals (41 normal controls, 85 subjects with impared fasting glucose (IFG) and 92 subjects with newly diagnosed T2DM). Clinical and biochemical parameters were assessed after receiving consent. Netrin-1 levels were determined by commercial enzyme-linked immunosorbent assay. Spearman correlation analyses and multivariable-adjusted linear regression analyses were conducted to examine the relationship between serum netrin-1 levels and glycometabolic parameters.

Results: Serum netrin-1 levels in subjects with IFG or T2DM was significantly higher than in normal control subjects (mean netrin-1 level; normal, IFG, and T2DM; 275.3, 436.5 and 441.0 pg/mL, respectively; p < 0.001). Serum netrin-1 levels had a significant positive correlation with fasting glucose, HbA1c, HOMA-IR, RST and ALT. Meanwhile, statistically inverse correlation was found between netrin-1 and HDL cholesterol and eGFR levels. In addition, serum netrin-1 was independently associated with the presence of IFG or T2DM after adjusting covariates and potential confounders. In terms of the AUC, serum netrin-1 levels presented an AUC of 0.784 for the prediction of IFG or T2DM.

Conclusions/Interpretation: Our results suggest that netrin-1 may be a new biomarker for early detection for IFG or T2DM (Clinical trial no. NCT02858030).

The Visceral Adiposity Index Is a Significantly Stronger Predictor of Incident Diabetes in Men than in Women

CHRISTOPH H. SAEYE, ALEXANDER VONBANK, CHRISTINE HINZE, DANIELA ZANOLIN, BARBARA LARCHER, ARTHUR MADER, ANDREAS LEHREMER, AXEL MUENDEL, HEINZ DREXEL, Berne, Switzerland; Feldkirch, Austria; Trieren, Liechtenstein, Philadelphia, PA.

The visceral adiposity index (VAI) is a validated tool for the evaluation of visceral adiposity, using waist circumference, serum triglycerides, age and gender to diagnose this metabolic abnormality. We aimed at investigating the power of the VAI to predict diabetes incidence in men and women. We prospectively recorded diabetes incidence in a large consecutive cohort of 1,022 patients undergoing coronary angiography for the evaluation of established or suspected coronary artery disease who did not have diabetes at baseline. The VAI was calculated according to the Amato formula; diabetes was diagnosed according to ADA criteria. At baseline, the VAI score did not differ significantly between men (n=845) and women (230±199 vs. 238±239; p=0.247). Prospectively, 133 patients newly developed diabetes during a follow-up period of 3.7±0.9 years; diabetes incidence did not differ significantly between men (23.0-24.9 kg/m2, the age-standardized prevalence of diabetes among Asians was 23.0-24.9 kg/m2, the age-standardized prevalence of diabetes among Asians was 23.0-24.9 kg/m2, the age-standardized prevalence of diabetes among Asians was 23.0-24.9 kg/m2, the age-standardized prevalence of diabetes among Asians was 23.0-24.9 kg/m2, the age-standardized prevalence of diabetes among Asians was 23.0-24.9 kg/m2, the age-standardized prevalence of diabetes among Asians was 23.0-24.9 kg/m2, the age-standardized prevalence of diabetes among Asians was 23.0-24.9 kg/m2, the age-standardized prevalence of diabetes among Asians was 23.0-24.9 kg/m2, the age-standardized prevalence of diabetes among Asians was 23.0-24.9 kg/m2, the age-standardized prevalence of diabetes among Asians was 23.0-24.9 kg/m2, the age-standardized prevalence of diabetes among Asians was 23.0-24.9 kg/m2, the age-standardized prevalence of diabetes among Asians was 23.0-24.9 kg/m2, the age-standardized prevalence of diabetes among Asians was 23.0-24.9 kg/m2, the age-standardized prevalence of diabetes among Asians was 23.0-24.9 kg/m2, the age-standardized prevalence of diabetes among Asians was 23.0-24.9 kg/m2, the age-standardized prevalence of diabetes among Asians was 23.0-24.9 kg/m2, the age-standardized prevalence of diabetes among Asians was 23.0-24.9 kg/m2, the age-standardized prevalence of diabetes among Asians was 23.0-24.9 kg/m2, the age-standardized prevalence of diabetes among Asians was 23.0-24.9 kg/m2, the age-standardized prevalence of diabetes among Asians was 23.0-24.9 kg/m2, the age-standardized prevalence of diabetes among Asians was 23.0-24.9 kg/m2, the age-standardized prevalence of diabetes among Asians was 23.0-24.9 kg/m2, the age-standardized prevalence of diabetes among Asians was 23.0-24.9 kg/m2, the age-standardized prevalence of diabetes among Asians was 23.0-24.9 kg/m2, the age-standardized prevalence of diabetes among Asians was 23.0-24.9 kg/m2, the age-standardized prevalence of diabetes among Asians was 23.0-24.9 kg/m2, the age-standardized prevalence of diabetes among Asians was 23.0-24.9 kg/m2, the age-standardized prevalence of diabetes among Asians was 23.0-24.9 kg/m2, the age-standardized prevalence of diabetes among Asians was 23.0-24.9 kg/m2, the age-standardized prevalence of diabetes among Asians was 23.0-24.9 kg/m2, the age-standardized prevalence of diabetes among Asians was 23.0-24.9 kg/m2, the age-standardized prevalence of diabetes among Asians was 23.0-24.9 kg/m2, the age-standardized prevalence of diabetes among As...
Results: We included 3850 subjects aged 60 years and older (37% male; 63% female; mean age 69.5 ± 6.5 years, BMI 28.7 ± 5.4 kg/m²). Among these, 1740 (45.2%) were classified as diabetic, 1140 (29.5%) as prediabetic, and 970 (25.3%) had normal glucose tolerance. In this population, 1HrPG, 2HrPG, and HbA1c were significantly associated with diabetes and the metabolic syndrome (MetS).

Conclusions: The large relative skeletal muscle mass has a potential preventive effect on developing diabetes, independently of glycemic parameters. In particular, in subjects with IFG who are at high risk for diabetes, larger relative skeletal muscle mass may provide a substantial benefit to prevent diabetes.

**Glucose Variability of Individuals without Diabetes Using a Long-Term Continuous Glucose Monitoring System**

DOROTHEE DEISS, TAHMID ABTAHI, RAVI RASTOGI, E.L. KELLEY, Berlin, Germany, Germantown, MD

Background: Prior investigations regarding glucose variability in nondiabetic subjects measured by continuous glucose monitoring (CGM) have been limited to only few weeks. Little is known about what defines healthy or pathologic glycemic variability. This study investigated “normal glycemia” under daily conditions using a long-term implantable CGM system in nondiabetic adults for 90 days.

Methods: 25 adult nondiabetic participants (10 Male, 15 Female, 17 participants >45 years old) were inserted with the Eversense® CGM System (Sens塘otics Inc, MD). Participants were instructed to continuously wear the CGM system during the 90 day period and calibrate the system when prompted. Analysis was performed to estimate standardized measures of euglycemia (<70-180 mg/dL), hypoglycemia (<54, <70 mg/dL), hyperglycemia (>180, >200 mg/dL) and glucose variability (Mean, SD, CV).

Results: Out of 25 participants, 3 had inadequate data for inclusion. Analysis showed the average glucose value of the nondiabetic participants was 102 mg/dL (SD=18 and CV=0.17). Average percent time spent in hypoglycemia (<54mg/dL was 0.14% and <70mg/dL was 1.5%. Time spent in euglycemia 70-180 mg/dL was 98%. Time spent in hyperglycemia (>180 and >200 mg/dL was 0.17% and 0.05%, respectively. 17 participants had at least one value <54mg/dL and 18 participants had glucose values >80mg/dL with 11 subjects with glucose values >200mg/dL.

Conclusions: Glycemic variability recorded over extended period of time in participants without a diagnosis of diabetes showed similar results as observed by previous researchers over short duration with tight glycemic control. However, hypo- and hyperglycemic excursions are in some normoglycemic regarded individuals more frequent than suggested without CGM. Further analysis including meal challenge and fasting levels may provide guidance regarding expected values for persons without a diagnosis of diabetes and to set realistic target ranges for those with diabetes.

**Exocrine Pancreatic Function as a Novel Biomarker in Pre-T1D**

JAMES J. ROSS, CLIVE WASSERFALL, DANIEL J. PERRY, KIERAN M. MCGRAIL, AMANDA J. POSSAL, TODD M. BRUSKO, DESMOND SCHATZ, MICHAEL J. HALLER, MARK A. ATKINSON, Ocala, FL, Gainesville, FL

Recent studies demonstrated reduced serum trypsinogen levels as well as pancreatic weight/volume in patients with type 1 diabetes (T1D) and non-diabetic/antibody (AAb)-positive subjects. Histological defects including increased CDP T cell infiltration and elevated CD4+ deposition have been observed in the exocrine T1D pancreas. Like trypsinogen, amylase and lipase are produced by the exocrine pancreas and serve as more common markers of exocrine function. We hypothesized that amylase and lipase levels would be lower in patients with T1D as well as in subjects with multiple (i.e., ≥2 T1D-related AAb) compared with controls. To test this, serum amylase and lipase levels were determined in 70 patients with recent-onset T1D (duration <3 mo), 57 patients with established T1D (duration >3 mo), 56 single AAb-positive (1AAb+) subjects, 42 multiple AAb-positive (≥2AAb+) subjects, 96 AAb-negative (AAb-) relatives of T1D patients, and 110 AAb- control subjects. Amylase levels, which are independent of age (r = -0.02, P = 0.7), were significantly lower in patients with T1D (mean ± SD 39.98 ± 17.8 mg/mL; P < 0.005) vs. AAb− subjects (47.40 ± 20.17 mg/mL). Lipase levels, which are positively correlated with age (r = 0.30, P < 0.0001), were significantly lower in T1D patients.
1544-P
Racial Differences in the Correlation of HbA1c to Early and Late Postprandial Glycemic Responses in Adults with Prediabetes

DANIEL S. HSIA, KARA MARLATT, COURTNEY M. PETERSON, ERIC RAVUSSIN, Baton Rouge, LA, Birmingham, AL.

Fasting plasma glucose (FPG), 2-hour oral glucose tolerance test (OGTT), and hemoglobin A1c (HbA1c) are used to screen for prediabetes and diabetes. While HbA1c testing offers the convenience of a simple blood draw without fasting, it is known to have confounders such as age, race, and red blood cell turnover rate to name a few. Furthermore, dynamic tests such as the OGTT and mixed-meal tolerance test (MMTT) are usually better at detecting p-cell dysfunction and insulin resistance when insulin is measured. We sought to determine how well HbA1c values correlated with glucose levels during a MMTT and whether the correlation varied by race. Baseline data from a clinical trial of 59 adults [27 white and 32 African American (AA)] with prediabetes defined as either FPG of 100-125 mg/dL and/or HbA1c of 5.7-6.4% were used. In this cohort, we correlated HbA1c to glucose levels at 30 and 120 mins after ingesting a standardized meal (smoothie) of 400 kcal (20% protein, 40% fat, and 40% carbohydrate). Mean FPG was higher in white participants (108±10 mg/dL) compared to AA participants (102±10 mg/dL) (p<0.05), but HbA1c was negatively correlated with glucose 30-mins post-meal (r=-0.46, p<0.03) but did not in AA participants (r=-0.11, p=0.53). In AA participants, HbA1c correlated with glucose (120-mins post-meal (r=-0.48, p<0.01) but did not in white participants (r=0.22, p=0.28). Thus, in this cohort, white adults with prediabetes showed greater impairment of fasting glucose than AA adults, despite lower HbA1c levels. Moreover, a higher HbA1c correlated with an impaired early glycemic response in white adults; whereas, a higher HbA1c correlated with impaired glucose tolerance in AA adults. These results may suggest racial differences in early vs. late postprandial responses that should be accounted for when screening for prediabetes and diabetes.

Supported By: National Institute of Diabetes and Digestive and Kidney Diseases (R01DK082675) to E.R.

1545-P
Diagnostic Accuracy in LADA—Low Correlation between Primary Care Physicians (PCPs) and an Endocrinologist

ALDO DE FERRARI, FERNANDO OVALLE, Birmingham, AL.

Background: Patients with LADA benefit from different interventions than those with T2D. However, distinguishing one entity from the other may be challenging in individual patients. We hypothesized that LADA is being underdiagnosed by PCPs.

Methods: We retrospectively reviewed the medical charts of 1257 patients that consecutively presented to our diabetes clinic from 2001-10. Inclusion criteria were: age >18 years, having diabetes, and having been assessed by one of our investigators upon presentation. We collected demographic, clinical, and laboratorial data from their first visit to our clinic.

Findings: Of 1257 only 6 (0.5%) were referred to our clinic with a diagnosis of LADA. In contrast, we identified a total of 133 individuals with LADA (10.6%). There was good correlation between PCPs and an endocrinologist in the diagnosis of common diabetes subtypes like T1D and T2D, but it was poor for less common diabetes subtypes including LADA (Table). Most of the patients with LADA were originally classified as T2D (n=105). Seven percent of patients with LADA in our population had a history of DKA.

Interpretation: LADA is currently being underdiagnosed by PCPs. Strategies to raise awareness of the existence of this patient population as well as cost-effective strategies to identify them are largely needed.

Supported By: National Institutes of Health (AI-42288); National Institute of Diabetes and Digestive and Kidney Diseases (UDP9K110120-01 to D.S., M.J.H., M.A.A.); JDRF (2-2012-280 to T.M.B., Jeffrey Keene Family Professorship)

1546-P
The Progression of Hyperglycemia and Diabetes Before and After Lung Transplant

DIVYA AKSHINATA, EVANA VALENZUELA SCHERER, ANDRES FELAÉZ, SATISH CHANDRASHEKARAN, TIAGO MACHUCA, JULIO A. LEY, Gainesville, FL.

Diabetes mellitus (DM) is a frequent complication of organ transplantation. The aim of the study was to determine the incidence and prevalence of DM after Lung Transplant (Ltx). Methods: Chart review of patients undergoing Ltx at the University of Florida, Gainesville between 2013 and 2015. Variables such as diabetes status before and after Ltx, glucose level (G) during first seven days after Ltx, insulin therapy and other relevant factors were included. Results: There were 81 Ltx surgeries corresponding to 78 patients (3 had repeat Ltx). Prior to Ltx 14 patients had DM (5 CF), only 2 them were taking insulin, both had G>200 mg/dl and <70 mg/dl were observed in 71% (58/81) and 19% (16/81) patients during the first 7 days after Ltx respectively. At Ltx surgery discharge, 35% (28/81) were on insulin, 51% of them (15/29) on basal insulin alone or in combination. After 12m from Ltx, 26 were on insulin, 69% of them (18/26) on basal insulin alone or in combination. Among those who had G>200mg/dl within the first 7 days, only 19% (5/26) had been diagnosed of DM before Ltx, and 45% of them (26/58) were taking DM medications 12 months after Ltx and 65% (17/26) were using basal insulin alone or in combination. Conclusion: Inpatient hyperglycemia is very common after Ltx. Use of insulin at discharge is a strong predictor for use of insulin 12m after Ltx, indicating the need for close monitoring.

Table. Prevalence of Diabetes Subtypes in 1257 Patients as Diagnosed by PCPs and an Endocrinologist.

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Prevalence according to PCPs</th>
<th>Prevalence according to endocrinologist</th>
<th>Pearson’s correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic-fibrosis related</td>
<td>0.8 (10)</td>
<td>1.0 (12)</td>
<td>0.91</td>
</tr>
<tr>
<td>type 1 diabetes, % (n)</td>
<td>22.3 (280)</td>
<td>24.3 (305)</td>
<td>0.78</td>
</tr>
<tr>
<td>type 2 diabetes, % (n)</td>
<td>70.5 (886)</td>
<td>49.6 (624)</td>
<td>0.62</td>
</tr>
<tr>
<td>LADA, % (n)</td>
<td>0.5 (8)</td>
<td>10.6 (133)</td>
<td>0.16</td>
</tr>
<tr>
<td>Other subtypes, % (n)</td>
<td>5.9 (75)</td>
<td>14.5 (183)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

1547-P
Falsely Decreased HbA1c in Diabetic Patient due to Dapsone

KHALED ALJAEAE, SALIMAH HAJI ALI, AGNIESZKA PAZDERSKA, Dublin, Ireland

HbA1c and fructosamine are glycated proteins used to monitor glucose control over time in patients with diabetes. Many factors can affect HbA1c values leading to spuriously low or elevated results. We report a case of a 67 year old woman with type 1 diabetes with good glycaemic control based on HbA1c values ranging from 44-52 mmol/mol over 7 year follow-up. She was commenced on dapsone for treatment of granuloma anulare; four months into this treatment her HbA1c was 25 mmol/mol. The record of self-monitoring blood glucose showed that most of her glucose values were within the recommended target. She had normal glycohaemoglobin awareness and reported only 3 episodes of symptomatic hypoglycaemia in the preceding four months. Given the history of dapsone therapy and the discordant result of self-monitoring blood glucose and HbA1c concentrations, we suspected methemoglobinemia as a cause.

Dapsone treatment has been recognized to cause falsely low HbA1c results by two mechanisms: haemolysis by reducing the erythrocyte life span and the formation of methemoglobin which interferes with HPLC used to measure HbA1c.

In conclusion, dapsone is commonly used in diabetic patients who have no autoimmune diseases. HbA1c monitoring in patients treated with—
sone is unreliable and other markers such as capillary blood glucose records, and other glycated proteins such as fructosamine should be used as an alternative for monitoring of glucose control is such patients.

Table. Laboratory Result.

<table>
<thead>
<tr>
<th>Prior to dapsone</th>
<th>4 months after dapsone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb level (g/dl)</td>
<td>13.2</td>
</tr>
<tr>
<td>MCV (fl/cell)</td>
<td>92</td>
</tr>
<tr>
<td>Absolute reticulocyte counts (10^9/L)</td>
<td>53</td>
</tr>
<tr>
<td>Total bilirubin level (micro/L)</td>
<td>13</td>
</tr>
<tr>
<td>Methaemoglobin fraction (%)</td>
<td>4.7</td>
</tr>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>X</td>
</tr>
</tbody>
</table>

Cardiometabolic Disease Risk Assessment Predicts Incident Diabetes in a Large and Diverse Population
LUKA WILKINSON, TAPAN MEHTA, W. TIMOTHY GARVEY, Birmingham, AL.

Background: Risk scores for predicting type 2 diabetes mellitus (T2DM) have been developed, but few have included adequate African-Americans. Objective: To derive and validate scoring systems to predict future diabetes in populations including caucasian- and African-Americans, weighted by sex and race.

Design, Setting, and Participants: We estimated 9.5-year risk of T2DM in participants with valid follow-up data taken from 12,1221 people in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, and externally validated it in 9,712 participants from the Atherosclerosis Risk in Communities study.

Methods: Cardiometabolic disease scores were calculated for each sex-race pair using quantitative clinical data. Incidence diabetes was defined as fasting glucose ≥ 126 mg/dl, non-fasting glucose ≥ 200mg/dl, currently on medication for T2DM, or self-report. Covariates included: sex, race, and age; waist circumference; blood pressure; HDL cholesterol; fasting triglycerides or on lipid-lowering medication. We assigned a simple integer score for each risk factor component using logistic regression coefficients for each sex-race pair. Discrimination was assessed with area under the receiver operating characteristic curves (AROCs).

Results: Diabetes incidence rates at a median follow-up of 9.5 years were 16.3% and 18.7% in African-American men and women, and 12.3% and 9.2% in caucasian-American men and women. Weighted covariates differed more by race than sex (p = 0.001). The AROCs ranged from 0.72 for black men to 0.78 for white women. External validated models performed well: AROC was 0.75 (black men) to 0.83 (white women).

Conclusion: The weighted CMDS score has high model discrimination using readily available clinical data, and can be used to quantify T2DM risk based on race- and sex-specific data; thus, diabetes prevention can be targeted to high risk individuals in a manner that optimizes outcomes, benefit-risk ratio, and cost-effectiveness.

Supported By: National Institutes of Health (T32HL105349)

Impact of the Structured, Comprehensive Clinic-Led, Population-Targeted Diabetes Intervention Program as Compared with the Standard Care Approach
INDUMATHI KUBERAN, SAMEER RAO, NAVNEET WADHWA, Mumbai, India, Delhi, India.

We implemented a structured comprehensive Diabetes Management Plan (DMP) which includes monthly diabetologist counselling, pharmacological interventions, dietician review and education, follow-up through face to face and mobile technology, exercise motivation and periodic investigations, at a one-time enrolment cost. ANOVA, Chi-Square test were used for the statistical analysis. We conducted a retrospective analysis of the glycemic measures of effectiveness in patients enrolled with DMP (n=47, males=32, females =15; mean age (years) 50.4 ± 9.4, min 27, max 72) compared to the group receiving the conventional Standard Of Care (SOC) over one year (n=47, males=24, females = 23; mean age (years) 54.3 ± 13.9, min 22, max 78; [p=0.116] from Jan-Dec 2017. At end of one year of follow-up, DMP group (baseline HbA1c 9.1±1.5%) demonstrated higher HbA1c reductions of 1.86±1.0% as compared to the SOC group (baseline HbA1c 9.5±1.5%), which was statistically significant (p=0.046). DMP group (baseline Fasting Blood Glucose (FBG) 167.5±59.32 mg/dl) demonstrated higher FBG reductions of 34.89 ± 7.69 which was highly statistically significant from baseline (p=0.001). However, FBG was not statistically significant as compared to the baseline within the SOC group (baseline 147.25 ± 52.11 mg/dl, [p=0.602]; the differences were statistically significant (p=0.050). The dyslipidemia parameters reveal that there was no significant difference in the groups for the change in LDL-C (p=0.36), total cholesterol (p=0.16) and HDL-C (p=0.11). The DMP group had significant elevation in HDL-C (11.8%, [p=0.001]). DMP with compulsory periodic interventions is useful as a better glycmic management tool and resource optimisation, as done in DMP in an emerging economy would be useful model to emulate even for the developed world to manage the cost of diabetes care.

Epidemiology—Diabetes Complications

Moderated Poster Discussion: Diabetes Complications (Posters: 1550-P to 1555-P), see page 19.

1550-P

Higher Rates of Celiac Disease Serology and Biochemical Markers in Adults with Type 1 Diabetes
FARID H. MAHMUD, ANTOINE B. CLARKE, KARIYAM C. JOACHIM, ESTHER AASSUR, AMISH PARikh, ANDREW ADVANI, BRUCE A. PERRINS, BAJALI R. SHAH, CAROLINE S. ZIUDUIDUK, CHARLOTTE MCDONALD, DAVID MACK, DROR KOLTN, EUGENE HSIIEH, EVA M. SZENTORGYGRI, SR, FRED SAIBIL, GEEHA MUKERJI, HEATHER A. LUCHNAN, JEREMY GILBERT, KENNY BAX, MARGARET L. LAWSON, MELANIE D. BEATON, NAV A. SALKODEJ, OLIVIA LOU, PATRICIA H. GALLIEDO, ROBYN L. HOULEN, RONNIE AROSON, SUSAN E. KIRSCH, WILLIAM G. PATERSON, ZUBIN PUNTHAKEE, MARGARET A. MARCON, TORONTO, ON, Canada, Mississauga, ON, Canada, Ottawa, ON, Canada, London, ON, Canada, New York, NY, Kingston, ON, Canada, Markham, ON, Canada, Hamilton, ON, Canada.

Background: Celiac Disease (CD) is more common in individuals with type 1 diabetes (T1D) and is frequently asymptomatic. Despite this association, evidence as to the impact and diagnostic accuracy of CD screening is limited in asymptomatic patients with T1D.

Objective: To describe CD serology and biochemical positivity rates in T1D patients screened as part of the Celiac Disease and Diabetes Intervention Evaluation Trial (CD-IDEAT).

Methods: Prospective data from patients, aged 8-45 years, with T1D screened at 22 sites across Ontario, Canada as part of CD-IDEAT were analyzed with respect to demographics, clinical symptoms and CD status. Serological and biopsy-confirmed rates of CD were evaluated.

Results: Overall, 2386 patients were approached and 2386 patients completed serological testing using tissue transglutaminase antibodies. The sample included 1298 (54.4%) adults, aged 19-45 years, and 1088 (45.6%) pediatric subjects, aged 8-18 years. Mean age was 23.1 ± 10.3 years, 49.2% female, with mean duration of diabetes 12.2 ± 9.9 years. A small number of screened patients (N=45) were symptomatic for CD as per study criteria with clinical GI symptoms (n=39), osteoporosis (n=2), aphous ulcers (n=1), weight loss (n=1), and/or anemia (n=2). Overall, 140 asymptomatic patients were serologically positive for CD. A positive CD serology rate of 7.2% (94/1298) was seen in adults as compared to 4.2% (46/1088) in pediatric subjects (p=0.034). Endoscopy was completed in 104 patients and CD was subsequently confirmed using duodenal biopsy in 54/71 adults (76.1%) and 28/33 pediatric patients (84.8%), with overall biopsy positivity rates of 4.2% and 2.6% respectively (p=0.034).

Conclusions: Significant differences were observed in CD serology and biopsy positivity, with higher rates seen in adults as compared with children with T1D, which may be due to increasing risk of autoimmune co-morbidities with age as well as many adults being naive to celiac disease screening.

Supported By: JDRF Canada

1551-P

Different Course of the Microvascular Complications of Diabetes Mellitus in Kidney Transplant Recipients with Posttransplant Diabetes—A Longitudinal Study
THIZA M. LONDONO GAI, LUANA S. GIARETTA, ROBERTO C. MANFRO, LUIS H. CANAVI, DANIEL LAVINSKY, CRISTIANE B. LEITAO, ANDREA BAUER, Ponto- lague, Brazil.

Objective: This study assessed microvascular complications (MC) occurrence in renal posttransplant diabetes mellitus (PTDM).

Methods: Patients ≥ 8 years of PTDM were included from a cohort of 895 kidney recipients (KR) transplanted in 2000-2011. Diabetic retinopathy (DR) was evaluated by fundus photographs (FP) and optical coherence tomography (OCT). Diabetes kidney disease was evaluated by protein to creatinine ratio (PCR) and eGFR. Distal polyneuropathy (DPN) was assessed by Michi-
Cis-Vaccenic Acid Is Associated with Lower HOMA-IR and Incident T2D in Participants from the MESA Cohort

NATALIE L. WEIR, LISA JOHNSON, WEIHUA GUAN, BRIAN STEFFEN, LUC DJUSSE, KENNETH J. MUKAMAL, MICHAEL Y. TSAI, Minneapolis, MN, Plymouth, MN, Boston, MA, Brockline, MA

The de novo lipogenesis pathway may play a key role in metabolic regulation. The omega-7 monounsaturated fatty acid cis-vaccenic acid (VA) is an endogenous downstream product of this pathway, and in vitro studies have suggested that it may downregulate gluconeogenesis and liver fat accumulation. However, it has been inconsistently shown to be associated with lower risk of type 2 diabetes (T2D). Previous studies have been in primarily homogeneous cohorts with few studies examining its effects on insulin resistance. Therefore, we aimed to evaluate if VA is associated with HOMA-IR and risk of incident T2D in 5,889 participants of the Multi-Ethnic Study of Atherosclerosis (MESA).

Phospholipid fatty acid profiles were determined by GC-FID. A multivariable linear regression model adjusted for age, sex, BMI, education status, smoking, ever used alcohol, and race/ethnicity was used to determine associations between baseline VA levels (quartiles) and HOMA-IR; a Cox proportional hazards model estimated risk of incident T2D over a median 12 year follow-up (n cases=663).

Individuals in the three upper quartiles of VA had a significantly lower log HOMA-IR compared to those in the reference quartile (Q1) (coefficient, [p-value]): Q2: -0.13 [p<0.001]; Q3: -0.22 [p<0.001]; Q4: -0.32 [p<0.001]. Race stratified analysis showed similar results for Chinese, black, and Hispanic but not white participants. Test for interaction shows the difference between Chinese and whites is statistically significant (p<0.001).

In a multi-racial cohort, VA demonstrated graded associations with lower insulin resistance and risk of diabetes. More studies are needed to elucidate the roles of VA and the de novo lipogenesis pathway in glycemic regulation.

Supported By: National Heart, Lung, and Blood Institute

WITHDRAWN

Type 2 Diabetes Mellitus and Renal Impairment in Real-World with Large Outpatient Electronic Medical Records—Antihyperglycemic Medication Dose Adjustment

SANG MO HONG, CHEOL-YOUNG PARK, Gyeonggi, Republic of Korea, Seoul, Republic of Korea

Objective: To estimate the level of inappropriate dosing of DPP-4 inhibitors, and to assess the level of emergency room visits, hypoglycemia, and mortality according to inappropriate dosing of DPP-4 inhibitors in type 2 diabetes (T2DM) patients with renal impairment (RI).

Research Design and Methods: Retrospective database analysis using the National Health Insurance Service Database and the General Health Examination Database in Korea. Patients aged ≥40 years with evidence of T2DM (ICD-9-CM codes from E10.x-E14.x) January 1, 2009 to December 31, 2015. Renal impairment defined with estimated with the Modification of Diet in Renal Disease (MDRD) GFR equation. To estimate the level of inappropriate dosing of DPP-4 inhibitors in RI was according to daily prescribed dose. And incidence of emergency room visits, hypoglycemia, and mortality were assessed using the hazard ratios (HRs) estimated with logistic regression model.

Results: In our study, we analysis 161,760 patients with T2DM and RI. Among them DPP-4 inhibitors were prescribed to 44222 patients (27.3%). DPP-4 inhibitor prescribed 21.44% in GFR<30 and 32.28% in 30≤GFR<50. In observation period, percentages of inappropriate dosing of DPP-4 inhibitors in T2DM with RI was 31.9%. The age and sex adjusted HR with 95% confidence interval (CI) for appropriate dosing of DPP-4 inhibitors compared with inappropriate dosing of DPP-4 inhibitors was 0.671(0.842,0.9) for emergency room visits, 0.819(0.748,0.898) for sever hypoglycemia, and 0.775 (0.717,0.839) for mortality.

Conclusions: Renal impairment is common but often undetected in patients with T2DM. In Korea, one of three patients with T2DM and RI received inappropriate doses, and they were associated with high risk of emergency room visits and sever hypoglycemia, and higher mortality. Further analyses to understand the clinical and economic consequences of these findings are needed.
quality of life. However, little is known about the secular trend of diabetes comorbidities in the last 20 years. Sample-weighted prevalence of twelve common comorbidities of diabetes was estimated using data from 52,842 adults aged ≥18 years who had diabetes in the National Health Interview Survey from 1997 through 2016, with age-standardized to the 2000 U.S. population. We ranked the prevalence (%) of twelve diabetes comorbidities including hypertension (47.8 to 59.7), asthma (13.2 to 21.8), cancer (7.6 to 10.4), and liver cirrhosis (3.0 to 4.1) continually increased (P<0.05), while CHD (15.4 to 13.4), COPD (10.1 to 8.0), and hepatitis (5.5 to 2.9) declined (P<0.05). Such trends were similar among subgroups stratified by gender or by race. In the past two decades, along with continuing increase of diabetes, the rates of its comorbidities including hypertension, asthma, cancer, and liver cirrhosis showed increasing trends, whereas the rates of CHD, COPD, and hepatitis exhibited decreasing trends in the U.S. adults.

**Table. Adjusted Progression Rates per 1,000 Person-Years**

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Baseline Category</th>
<th>Progression Rate (per 1,000 Person-Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hytension</td>
<td>A1&lt;30</td>
<td>A2=30−&lt;60</td>
</tr>
<tr>
<td></td>
<td>(no. of cases)</td>
<td>(no. of cases)</td>
</tr>
<tr>
<td></td>
<td>(per 1,000)</td>
<td>(per 1,000)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>190.7 (183.3−198.4)</td>
<td>200.4 (187.3−214.6)</td>
</tr>
<tr>
<td></td>
<td>(P=0.014)</td>
<td>(P=0.025)</td>
</tr>
<tr>
<td></td>
<td>Progression to Category G2</td>
<td>Progression to Category G3</td>
</tr>
<tr>
<td></td>
<td>8.6 (7.6−9.6)</td>
<td>14.4 (12.2−17.1)</td>
</tr>
<tr>
<td></td>
<td>(P=0.063)</td>
<td>(P=0.019)</td>
</tr>
<tr>
<td>Asthma</td>
<td>5.4 (4.6−6.3)</td>
<td>9.7 (7.9−11.9)</td>
</tr>
<tr>
<td></td>
<td>(P=0.008)</td>
<td>(P=0.002)</td>
</tr>
<tr>
<td>COPD</td>
<td>2.5 (2.0−3.2)</td>
<td>5.3 (4.0−7.0)</td>
</tr>
<tr>
<td></td>
<td>(P=0.028)</td>
<td>(P=0.002)</td>
</tr>
<tr>
<td>Cancer</td>
<td>0.8 (0.5−1.2)</td>
<td>1.5 (0.9−2.5)</td>
</tr>
<tr>
<td></td>
<td>(P=0.002)</td>
<td>(P=0.002)</td>
</tr>
</tbody>
</table>

**Incidence of Chronic Kidney Disease and Progression of Renal Dysfunction in Type 2 Diabetes—The Role of Albuminuria**

**Effects of Dulaglutide and Insulin Glargine on Estimated Glomerular Filtration Rate in a Real-World Setting**
Patients with DM, particularly T2D, are at high risk for BDGD, and clinicians should consider these disorders as potential comorbidities during DM management.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Incidence per 1,000 person-years (95%CI)</th>
<th>Point prevalence, % (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
<td>Type 1 diabetes</td>
<td>Type 2 diabetes</td>
</tr>
<tr>
<td>N=48,750,800</td>
<td>N=7,656</td>
<td>N=4,267,061</td>
</tr>
<tr>
<td>Overall</td>
<td>27.4 (27.3-27.5)</td>
<td>44.2 (42.7-45.6)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18</td>
<td>6.4 (6.3-6.5)</td>
<td>17.6 (16.9-19.3)</td>
</tr>
<tr>
<td>18-44</td>
<td>153,852 (1.3)</td>
<td>344 (1.5)</td>
</tr>
<tr>
<td>45-54</td>
<td>24.3 (24.2-24.3)</td>
<td>62.9 (60.5-65.3)</td>
</tr>
<tr>
<td>55-64</td>
<td>347,615 (2.7)</td>
<td>2,201 (6.3)</td>
</tr>
<tr>
<td>≥75</td>
<td>225,389 (4.4)</td>
<td>n/a</td>
</tr>
</tbody>
</table>

* Number of individuals with BDGD within respective population

Omega-6 Eicosadienoic Acid Is Associated with Lower HOMA-IR and Incident T2D in Participants from the MESA Cohort

NATALIE L. WEIR, WEIHUA GUAN, BRIAN STEFFEN, LYN M. STEFFEN, AMY B. KARGER, MICHAEL Y. TSAI, MNNEAPOLIS MN, Plymouth, MN

Linoleic acid (LA) and related omega-6 fatty acids have been implicated in contributing to metabolic dysfunction. However, there is some evidence to support that certain omega-6 fatty acids, such as eicosadienoic acid (EDA), may play a beneficial role in inflammation. Although, studies have inconsistently shown EDA to be inversely associated with insulin resistance and type 2 diabetes (T2D). The present study evaluated associations of EDA with log HOMA-IR and risk of incident T2D in 5,889 participants of the Multi-Ethnic Study of Atherosclerosis (MESA).

Phospholipid fatty acid profiles were determined by GC-FID. A multivariable linear regression model adjusted for age, sex, BMI, education status, smoking status, ever used alcohol, and race/ethnicity was used to determine associations between baseline EDA levels (quartiles) and log HOMA-IR, a Cox proportional hazards model estimated risk of incident T2D over a median 12-year follow-up.

Individuals in the three upper quartiles of EDA had a significantly lower log HOMA-IR compared to those in the reference quartile (p<0.001). After race stratification, all four races showed lower risk of incident T2D (p<0.001). During the analysis year, 78,067 patients with DM were identified, of which only 38,417 were documented as T1D and 1,747,161 as T2D. In general, incidence and prevalence rates of BDGD were 3-times higher in patients with DM (incidence, 82.7 vs. 27.4; prevalence, 10.3% vs. 3.4%), with T2D having 4-times the incidence and 3-times the prevalence of that in T1D (incidence, 186.8 vs. 44.2; prevalence, 13% vs. 4.4%).
Higher Dietary Intake of Vitamin D Is Associated with Lower Incidence of Diabetic Nephropathy in Japanese Patients with Type 2 Diabetes

CHIKA HIRIKAWA, REI AIDA, SHIRO TANAKA, SACHIKO TANAKA, CHEMI KAMADA, YUKIO YOSHIMURA, ATSUSHI ARAKI, TATSUMI MORIYA, SHIGEHIRO KATAYAMA, HIROHITO SUNE, WAGIJA, JAPAN, KYOTO, JAPAN, SHIBA, JAPAN, TOKUSHIMA, JAPAN, KYOTO, JAPAN, SAGAMIHARA, JAPAN, KAWAGU, JAPAN

Evidence for optimal dietary intake of vitamin D for prevention of diabetic complications is sparse although associations between low vitamin D intake and high incidence of diabetes and vitamin D supplementation and improvement in insulin resistance were reported. We aimed to investigate the relationship between vitamin D intake and the incidence of diabetes complications in Japanese patients with type 2 diabetes aged 40-70 years with HbA1c 6.5%. The present analysis was conducted as a multicenter prospective study on the incidence of and risk factors for macro- and microvascular complications among 2205 Japanese patients with type 2 diabetes from outpatient clinics in 59 university and general hospitals in Japan. Analyzed were 1516 responders to a baseline dietary survey assessed by the Food Frequency Questionnaire based on food groups. Primary outcome was the 8-year risk of nephropathy, retinopathy, and cardiovascular disease (CVD). Cox regression analyses estimated hazard ratios (HRs) for dietary intake adjusted for age, gender, body mass index, HbA1c, smoking, energy intake, and other confounders. Mean vitamin D intake in quartiles ranged from 5.4 to 18.7 μg/day. After adjusting for confounders, HRs of diabetic nephropathy in the 2nd, 3rd, and 4th quartiles for vitamin D intake compared with the 1st quartile were 0.7 (95% confidence interval 0.4-1.3, p=0.29), 1.2 (0.6-2.2, p=0.61), and 0.3 (0.14-0.79, p=0.01), respectively. There was no significant association of vitamin D intake with retinopathy and CVD in the 2nd to 4th quartiles relative to the first quartile (retinopathy: 1.2 (0.5-1.6, 0.4), 0.8 (0.5-1.2, p=0.23), and 0.7 (0.5-1.0, p=0.08); CVD: 1.1 (0.7-1.7, p=0.83), 1.2 (0.7-2.0, p=0.62), and 0.7 (0.4-1.3, p=0.22)). Findings suggested that high vitamin D intake was associated with a lower incidence of diabetes nephropathy among Japanese patients with type 2 diabetes.

Supported By: Japan Society for the Promotion of Science

Vascular Events in Patients with Type 2 Diabetes in the Year following Initiation of Second-Line Therapy—The DISCOVER Study

MIKHAIL KOSEBOGD, HUNJING CHEN, JAVIER CID-RUZAF, FETER FENICI, MARILLA B. GOMES, CAMILLE KHNUT, STUART POCON, WOLFGANG RATHMANN, MARINA V. SHESTAKOVA, ICHIRO SHIMOMURA, FILIP SURMONT, FENGSHENG TANG, HIROTAKA WATADA, LINQING JI, NIKLAS HAMMAR, Kansas City, MO, Gatersburg, MO, Barcelona, Spain, Cambridge, United Kingdom, Rio de Janeiro, Brazil, Leicester, United Kingdom, London, United Kingdom, Düsseldorf, Germany, Moscow, Russian Federation, Osaka, Japan, Luther, United Kingdom, Tokyo, Japan, Beijing, China, Malmö, Sweden

Background: Vascular complications are the main cause of death and disability in people with type 2 diabetes (T2D). We assessed the occurrence of complication during the first year of follow-up of DISCOVER, a global, observational study on the incidence of and risk factors for macrovascular complications in Japanese patients with type 2 diabetes initiating second-line glucose-lowering therapy.

Methods: Patients with data available at 6 or 12 months were included. Microvascular complications comprised new diagnoses or procedures related to retinopathy, neuropathy, nephropathy or erectile dysfunction. Macrovascular complications comprised new diagnoses or procedures related to coronary or peripheral artery disease or heart failure.

Results: In 11,430 patients from 34 countries, new microvascular and macrovascular complications were reported in 6.6% and 4.7% of patients, respectively, with substantial variations across countries (Figure). The proportion of patients with new microvascular complications was higher in those with vs. without microvascular disease at baseline (9.8% vs. 5.9%, p < 0.001). The same was observed for new macrovascular complications in patients with vs. without macrovascular disease at baseline (16.9% vs. 2.9%, p < 0.001).

Conclusions: Rates of new vascular complications over 1 year were strikingly high in presumably low-risk patients with short T2D duration, highlighting opportunities for early aggressive risk-factor modification.
Risk of Nonalcoholic Fatty Liver Disease (NAFLD)-Related Liver Complications in the Diabetic Population in Israel

INBAL GOLDSSTEIN, GAIL FERNANDES, GABRIEL CHODICK, SWAPNIL RAJPATHAK, AVRAHAM KARASIK, Tel Aviv, Israel; Kewalnoor, NJ, Ramat Gan, Israel.

In the absence of early non-invasive diagnostic tools, the burden of NAFLD and its related complications in the diabetic (DM) population remains unclear. Using longitudinal data and defined criteria to identify NAFLD patients, this study evaluated the incidence of NAFLD-related liver complications in DM vs. non-DM population. The study utilized the computerized database of a nationally representative payer-provider health fund, including all members enrolled in year 2000 (index) without viral hepatitis or excess alcohol intake. NAFLD was defined as at least 2 of the following criteria: ≥2 measurements of elevated liver enzymes (>2 upper normal limit), NAFLD fibrosis score ≥1.455, coded NAFLD Diagnoses, or imaging evidence using natural language processing of 1 million ultrasonography test reports. Cirrhosis, liver transplant and hepatocellular carcinoma (HCC), were detected by diagnoses, procedures, and the national cancer registry. DM was defined using a previously validated registry. Incidence density rates based on person-years (PY) since index were compared between NAFLD cases vs. age and sex matched controls (2:1 ratio). The incidence was further stratified by the presence of DM. The total population included 1,083,405 subjects with a mean follow-up of 15.1 years (SD=4.2). Out of these, n=61,644 were identified as NAFLD, with a mean age of 52.1 years (SD=13.6) and 23.4% with DM when they met the criteria for NAFLD. The incidence of cirrhosis, HCC and liver transplant was substantially higher in NAFLD cases as compared with matched controls with rate ratios of 5.6 (95% CI: 5.2-6.0), 1.3 (1.2-1.4) and 3.9 (2.9-5.2) respectively. After stratification by DM, rate ratios were 2.2 (95% CI: 2.0-2.3) for cirrhosis, 2.1 (1.9-2.5) for HCC and 2.5 (1.7-3.5) for liver transplant in NAFLD with DM vs. NAFLD without DM. This study shows that patients identified with NAFLD had higher rates of liver complications and these rates were increased among patients with DM.

Supported By: Merck & Co., Inc.

Meta-analysis of Serum Uric Acid (SUA) and Cardiovascular Events in Diabetes Population

YIXUE SHAO, HUI SHAO, LIZHENG SHI, New Orleans, LA

Background: Recent studies found elevated serum uric acid (SUA) level were associated with type 2 diabetes mellitus (T2DM) progression. However, whether SUA level was relevant to the development of cardiovascular events was inconclusive.

Objective: To explore the association between SUA level and risk of cardiovascular events and all-cause mortality among patients with T2DM.

Methods: A systematic literature search was conducted using the Web of Science and PubMed database (1980-2017). Search terms and strategies for PubMed were as follows: using [Title/Abstract] or [MeSH Terms] to search “diabetes,” “serum uric acid,” “cardiovascular disease,” and “all-cause mortality.” Studies that reported associations between SUA and cardiovascular events (i.e., coronary heart disease (CHD) and stroke), and all-cause mortality in patients with T2DM were identified, and these associations were extracted and converted into hazard ratio (HR) of cardiovascular events per 59 µmol/l SUA increase. Meta-analysis was conducted to synthesize the associations between SUA level and risk of cardiovascular events, using random effect model to account for possible study heterogeneity. Heterogeneity was assessed using I², and the meta-analysis was performed using Stata 12.0. This study was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.

Results: 6 (n=11,750 patients), 4 (n=3034 patients) and 2 studies (n=7792 patients) and 2 studies (n=7792 patients) were identified reporting associations between SUA level and all-cause mortality, CHD and stroke respectively. HR for all-cause mortality, CHD, and stroke per 59 µmol/l increase was 1.150 (95% CI: 1.134, 1.165), 1.032 (95% CI: 0.983, 1.021) and 1.177 (95% CI: 1.070, 1.284), respectively. Heterogeneity bias was found in the analyses. Overall, SUA were associated with higher risk of all-cause mortality and stroke. However, we found no significant association between SUA level and CHD among T2DM population.

Reduced Lower-Limb Muscle Strength in Type 2 Diabetes Patients with Arthritis Is Associated with Impaired Beta ‑Cell Function

DANA P. ZAHARIA, DOMINIK PESTA, PABLO BOBOV, YULIYA KUPRIYANOVA, KÁLMÁN BÓDAS, VOLKER BURKART, JONG ‑HEE HWANG, KARSTEN MÜSSIG, MICHAEL RODEN, JULIA SZENDROI, Düsseldorf, Germany

Insulin levels might affect the integrity of musculoskeletal structures. We hypothesized that in type 2 diabetes patients (T2D) with arthritis muscle ‑skeletal impairment is associated with insulin secretion. This analysis of the German Diabetes Study comprised T2D with T2D+A (n=1124) vs. T2D-A (n=1248), age 63±9 years, BMI 34.6±7.2 kg/m² or without arthritis (T2D-A: 222±13 ±10): 59±15 years, 33.8±6.5 kg/m² and lean controls (CON: 1810±8): 42±16 years, 25.3±4.1 kg/m². Group comparison analyses were adjusted for age, sex and BMI. T2D duration was ~5 years. Beta ‑cell function was assessed from C ‑peptide levels during glucagon stimulation test (GST) and intravenous glucose tolerance tests (IVGTT). Insulin sensitivity (IS) from hyperinsuline ‑euglycemic clamps. Isometric knee extension force (KEF) was assessed with a dynamometer and range of motion (ROM) was measured using a goniometer. IS was comparable in T2D-A and T2D-A (3.5±0.7 vs. 5.1±2.4 mg·kg⁻¹·min⁻¹), but lower than in CON (11.5±3.3 mg·kg⁻¹·min⁻¹; p<0.05). Hemoglobin Alc (HbA1c) was similar in T2D-A and T2D-A (53±6 vs. 51±11 mmol/mol), but higher than in CON (33±3 mmol/mol, p<0.05). In T2D-A, C ‑peptide secretion (IVGTT) was 43% and 63% lower (p<0.05) than in T2D-A and in CON, respectively. C ‑peptide secretion (IVGTT) correlated inversely with HbA1c levels in T2D-A (r=−0.81, p<0.05) and T2D-A (r=−0.60, p<0.05) in T2D-A, KEF was 65% lower than in CON (9±11 kg vs. 47±12 kg; p<0.05) and correlated negatively with HbA1c secretion (GST; r=−0.39, p<0.05). ROM was 8% and 19% lower (p<0.05) in T2D-A than in T2D-A and CON, respectively. Within T2D-A, ROM was negatively correlated with insulin secretion (IVGTT; r=−0.64, p<0.05).

In conclusion, musculoskeletal impairment is associated with decreased beta ‑cell function in T2D patients suffering from arthritis, possibly mediated by chronic hyperglycemia. Supported By: German Ministry of Culture and Science of the State of North Rhine ‑Westphalia; German Federal Ministry of Health; German Federal Ministry of Education and Research.
1568-P
Risk Factors Differ by First Manifestation of Cardiovascular Disease (CVD) in Type 1 Diabetes (T1D)
RACHEL G. MILLER, TREVOR J. ORCHARD, Pittsburgh, PA
CVD is a major contributor to T1D morbidity and mortality but presents in a variety of first manifestations. Thus we aimed to assess risk factors for 3 CVD manifestations in a T1D cohort: 1) major atherosclerotic cardiovascular event (MACE, i.e., CVD death, myocardial infarction (MI), stroke), 2) coronary revascularization, no prior MI (REV), 3) soft CVD (SOFT, i.e., ischemic CEG or anjila). Data are from the Pittsburgh Epidemiology of Diabetes Complications (EDC) study, an ongoing, prospective cohort study of childhood-onset (<17 years) T1D diagnosed 1950-80 with 25 years of follow-up (n=658, 48% women, mean age 27, T1D duration 18 years at 1988-88 baseline). Follow-up exams occurred biennially for the first 10 years and at 18 and 25 years. MACE and REV were ascertained by death certificate adjudication or self-report, confirmed with medical records. Angina was determined by EDC physician history and ischemia by Minnesota coded ECGs. Prevalent CVD cases (n=54) were excluded. Those experiencing each manifestation were compared to participants not developing any CVD over follow-up. Baseline (BL), time varying updated mean (UM) and time varying most recent (MR) risk factors were assessed in Cox models (HRs per unit). CVD first manifested as n=107 MACE, n=38 REV, and n=91 SOFT. In T1D duration-adjusted multivariable models, MACE was predicted by MR ln (albumin excretion rate (AER)) (HR 1.3 p<0.001), UM systolic blood pressure (SBP) (HR 1.03 p<0.001), BL smoking (HR 1.9 p=0.003), UM LDLc (HR 1.01 p=0.03) and UM HbA1c (HR 1.01 p=0.03). REV was predicted by BL LDLc (HR 1.03 p<0.001), BL estimated glomerular filtration rate (HR 0.98 p=0.002) and MR HbA1c (HR 1.3 p=0.03). SOFT was predicted by MR SBP (HR 1.03 p<0.001), UM ln/triglycerides (HR 1.8 p=0.01), MR HbA1c (HR 1.2 p=0.01) and MR ln/AER (HR 1.2 p=0.02). HbA1c was consistently, but modestly, associated with all CVD manifestations. Additionally, BP and AER are important predictors of MACE and SOFT, while REV is most strongly predicted by BL LDLc.
Supported By: National Institute of Diabetes and Digestive and Kidney Diseases (R01DK034818); Rossi Memorial Fund

1569-P
The Cuban Prospective Study—Diabetes and Cause-Specific Mortality in Cuba
SHAQUILLE J.C. CHARLES, Baltimore, MD
Introduction: Large-scale prospective studies of diabetes and cause-specific mortality have been conducted mainly in high-income countries, where there is good access to healthcare. However, there is limited evidence on the effect of diabetes on mortality in low- and middle-income countries, such as Cuba. Methods: From 1996-2002, we recruited 146,556 participants (aged ≥30) from the general population in Cuba into a prospective cohort study. We recorded the presence or absence of previously diagnosed diabetes, and monitored for deaths through December 31st, 2015. We estimated adjusted hazard ratios (HR) for cause-specific mortality at ages 30-84 years among participants who had diabetes at recruitment vs. those who did not have diabetes at recruitment; participants with prior chronic disease other than diabetes were excluded from the analyses. Results: At recruitment, the overall prevalence of diabetes was 4% in men and 7% in women, and the mean age was 53 (SD13) years. Previously diagnosed diabetes was associated with about twice the risk of all-cause mortality (HR 1.89 [95% CI 1.79-1.99], mean age at death 70 [SD12]). The association was stronger at younger ages, but did not differ by sex: HR 2.68 (2.29-3.14) at 30-59 years, 2.20 (2.03-2.38) at 60-74 years, and 1.56 (1.44-1.68) at 75-84 years. Diabetes was strongly associated with mortality from renal, cardiovascular and respiratory diseases, but not with cancer. The excess mortality associated with diabetes accounted for ~10% of all premature deaths (<75 years) in Cuba for 2015; mostly from cardiovascular disease. Conclusion: Despite limited resources in Cuba, the association of diabetes with all-cause mortality was similar to high-income countries and less extreme than in many other middle-income countries.

1570-P
Liver Fibrosis as Assessed by the FIB-4 Index in Patients with Type 2 Diabetes (T2DM)
CLAUDIA M. FILOZOF, STEPHEN JONES, BARRY J. GOLDSTEIN, Madrid; Spain, Maidenhead; United Kingdom, Princeton, NJ
Data about liver fibrosis in T2DM are scarce. The FIB-4 index is a non-invasive panel to evaluate underlying hepatic fibrosis. FIB-4 values ≥ 1.45 and ≥ 2.67 were reported to have a negative predictive value (NPV) of ~80% and PPV of~65% for advanced fibrosis. FIB-4 values ≥ 2.67 were reported to be associated with 16X increase in clinical outcomes in NAFLD. FIB-4 range ≥ 1.45 <2.67 is suggested to be an indeterminate area. We assessed FIB-4 values and their changes over 4 years in 334,076 patients (48% male) with T2DM. A total of 75.2%, 22.3%, 1.3% and 1.2% of subjects had FIB-4 ≥ 1.45, ≥ 2.67, > 2.67-3.25 (G3) and ≥ 3.25 (G4). Subjects with low FIB-4 were younger, had lower ALT/AST and higher platelet counts (Table). Almost 50% of the patients with FIB-4 ≥ 2.67 had ALT/AST within reference ranges (RR). Mean trauma Tg and HbA1c were similar among groups. Among 61 patients, 83% stayed G1, 16.3% progressed to G2 and 0.7% had FIB-4 ≥ 2.67 after 4 years. A total of 10% and 27% of patients initially in G2 and G3 progressed to FIB-4 associated with higher risk of liver outcomes. Conclusion: Only 75% of the patients had FIB-4 suggesting absence of advanced liver fibrosis, ~50% of patients at risk of liver outcomes had ALT/AST within RR. FIB-4 is a simple, inexpensive method that may help identify patients at risk of liver outcomes. Strategies to slow the growth of liver complications and therapeutic options are necessary to mitigate disease burden.

Table.

Age, liver Enzymes and Platelet Counts by FIB-4 range. Mean (SD)

<table>
<thead>
<tr>
<th>FIB-4&lt; 1.45</th>
<th>FIB-4=1.45&lt; 2.67</th>
<th>FIB-4=2.67&lt; 3.25</th>
<th>FIB-4≥ 3.25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>57.2 (10.8)</td>
<td>66.3 (8.4)</td>
<td>67.0 (7.4)</td>
<td>65.2 (8.0)</td>
</tr>
<tr>
<td>ALT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25.3 (15.0)</td>
<td>28.3 (21.2)</td>
<td>38.4 (33.9)</td>
<td>54.2 (52.2)</td>
</tr>
<tr>
<td>Platelet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>272.9</td>
<td>200.5</td>
<td>158.5</td>
<td>131.7</td>
</tr>
<tr>
<td>counts</td>
<td>(62.1)</td>
<td>(60.6)</td>
<td>(39.5)</td>
</tr>
</tbody>
</table>

1571-P
The Natural Course and Risk Factors for Progression of Diabetic Retinopathy—KNDP Prospective Cohort Study
HYUN UK MOON, JA YOUNG JEON, SOOJIN LEE, SEUNG JIN HAN, HAE JIN KIM, HONG CHUN, TAE HO KIM, YOUNG SEOL KIM, JEONG-TAE WOO, KYU JEUNG. AHN, MOONSUK NAM, SEI HYUN BAIK, YONGSOO PARK, KWANWOO LEE, Suyeon, Republic of Korea, Seoul, Republic of Korea, Seongsan, Republic of Korea, Incheon, Republic of Korea, Champaign, IL
Introduction: We investigated the annual incidence rate and risk factors for progression of diabetic retinopathy in The Korean National Diabetes Program. Method: The Korean national Diabetes Program (KNDP) is a prospective, multicenter, and observational cohort study performed on type 2 diabetic patients in Korea. The study started in May 2008 and continued to follow-up until March 2014. Of the 3,949 patients enrolled in the KNDP, we analyzed 2962 patients who had both eyes photographed and assessed at baseline and further follow-up. An ophthalmologist evaluated and graded the fundoscopic findings. Diabetic retinopathy (DR) was classified as 4 stages which were no DR, NPD5, PDR and blindness. We calculated the annual incidence rate from stage to stage. We analyzed the risk factor for progression of diabetic retinopathy.
Results: The mean follow-up time (SD) was 4.1 (1.7) years. The mean age and DM duration were 54.6 (9.8) years and 6.7 (5.6) years, respectively. The mean level of fasting glucose and HbA1c was 144 (50) mg/dl and 7.7 (1.7), respectively. Of those, patients with diabetic retinopathy was 691 (23.4%). The annual progression rate from no retinopathy to NPD5 was 3.28% (295/2271). Patients progressed directly from NPDR to PDR at a rate of 3.13% (85/2719). Three of 200 patients with PDR progressed to blindness, at an annual rate of 0.57%. Patients who further progressed retinopathy had older age, longer DM duration, higher levels of HbA1c, higher systolic blood pressure, and more history of cerebrovascular disease than those who didn’t progress retinopathy. Conclusion: We reported the results of larger scale on DR progression than previous study of Korea. When compared to previous studies, the disease progression has improved over the 2 decades in Korean patients with type 2 diabetes. Our findings are consistent with other recent small studies from Korea. This study also confirmed risk factors for DR progression.
1572-P
Microvascular Disease Burden and All-Cause Mortality in Type 1 Diabetes—A 10-Year Follow-Up Study
MONIA GAROFOLI, ROSA GIANNARELLI, MICHELE ARAGONA, DANIELA LUC-
CHESI, LAURA GIUSTI, VERONICA SANCHIO-BORNE, GIUSEPPE DANIELE,
ROBERTO MICCOLI, GIUSEPPE PENNO, STEFANO DEL FRATO, Iqsal italy.

Type 2 diabetes (T2D) is associated with a substantially increased risk of cardiovascular (CV) events and premature death. The effect of the microvascular disease (MD) burden, i.e., the cumulative burden of retinopathy, nephropathy and peripheral neuropathy on all-cause mortality was evaluated in 774 T1D age 40±11.7. DD 19.4±12.2 years; HbA1c 7.8±1.2% in a mean follow-up of 6.10±2.5 years. Distribution of MD: was no- MD: n= 425
(54.3%); MD1: 250 (32.3%); MO2: 75.9 (7.9%); MD3: 24 (3.1%). Distribution was unchanged after exclusion of MD T1D (6.3%) with previous CV events (CV: 57.0%, 32.2%, 8.5% and 2.3%, respectively. Compared to no-MD, MD1-3 groups showed an adverse CV risk profile with steeply increase in age, DO, BML, WHR, BP, Hba1c, uric acid and EOFRIDAB PCS risk score for major vascular conditions (p=0.0001); total and LDL cholesterol, and triglycerides (p<0.05). eGFR (CKD-EPOI) decreased, albuminuria progressively increased (p<0.0001). Rate of CV events and that of EOFRIDAB score ≥20 increased with MD: 1.6%, 5.6%, 17.3%, and 29.2%; 4.0%, 14.4%, 41.3% and 72.2%, respectively (p=0.0001). Consistently, subject of rates on BP-lowering agents, RAS-blockers, statins e anti-platelet drugs increased (p<0.0001). A total of 52 deaths occurred during the 8,184 person-years of follow-up (6.7%); 3.6±1000 person-years. Death rate increased with MD: no-MD: 1.9%; MD1: 6.8% (HR: 3.75, 95% CI 1.12-8.69); MD1 14.7% (7.10, 2.85-17.67); MD3 66.7% (45.64, 19.50-106.79, K-M, p<0.0001). Death rate was unchanged after exclusion of MD CV: 1.9, 6.4%, 12.9% and 64.7% (p<0.0001). After adjustment for age and sex, HRs were: MD1 2.56 (95% CI 1.11-6.14); MD2 3.42 (11.29-0.06); MD3 16.21 (6.20-42.35; p<0.0001). In fully adjusted model, HRs were: MD1 2.51 (95% CI 1.01-6.23); MD2 2.97 (1.07-8.25); MD3 9.68 (3.19-29.36; p<0.0001), with independent effects for age (HR 1.06), uric acid (HR 1.37) and smoking history (HR 2.45). Thus, the cumulative burden of MD independently affects the risk of all-cause death in T1D.

1573-P
Effects of Bariatric Surgery on FGF-19 and FGF-21 Levels on Obese Diabetic Women
SAHAR AZHARIAN, ALICE MURPHY, PHILIP G. MCTERNAN, MILAN K. PIYA,
GYANENDRA TRIPATHI, Coventry, United Kingdom, Nottingham, United Kingdom, Sydney, Australia, London, United Kingdom.

Background: Fibroblast growth factor 19 (FGF-19) and FGF-21 regulate glucose tolerance and insulin sensitivity, which in type 2 diabetes mellitus (T2DM) conditions becomes dysregulated. Whilst weight loss can restore this functionality, bariatric surgery can have a specific impact due to intestinal nutrient absorption and gut microbiota. We aimed to analyze the effects of different bariatric surgeries: sleeve gastrectomy (SG), laparoscopic adjustable gastric banding (LAGB) and biliopancreatic diversion (BPD) on changes in FGF-19 and FGF-21 levels.

Methods: Obese and T2DM women (n=41 BMI>35 Kg/m2) undergoing SG (n=14), LAGB (n=13), and BPD (n=14) participated in an ethics approved study. Serum samples were collected before and 6 months after surgery. FGF-19, FGF-21 levels and AT RNA oxidation product, 8-oxo-7,8-dihydroguanosine (8-oxoGuo), has been implicated in the development of kidney disease. We assessed whether endogenous sex hormones are associated with chronic kidney disease (CKD) in obese women. Whether endogenous sex hormones are associated with chronic kidney disease (CKD) is not known. We conducted a secondary analysis of longitudinal data from the DPPOS, the follow-up study of the Diabetes Prevention Program (DPP), a randomized trial of diabetes prevention that assigned participants to placebo, metformin, or lifestyle intervention. This analysis included overweight and glucose-intolerant men (n=888) and women (n=1281) not using exogenous sex hormones who had urine albumin-to-creatinine ratio (ACR) > 30 mg/g and normal estimated glomerular filtration ratio (eGFR) > 60 ml/min/1.73 m2.

Sex Hormones (dehydroepiandrosterone (DHEAS), dihydrotestosterone, testosterone, estradiol, estrone, and sex hormone binding globulin (SHBG)) were measured at baseline. CKD was defined as incident low eGFR and/or albuminuria ACR ≥ 30 mg/g. eGFR and ACR were measured annually over 11 years of DPPOS follow-up. Multivariable Cox regression models adjusted for eGFR and log-ACR, age, race/ethnicity, body mass index, blood pressure, insulin resistance, high-density lipoprotein, C-reactive protein, and use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers at baseline. At baseline, the mean (SD) of eGFR was 94 (15) ml/min/1.73 m2, and the median (IQR) of ACR was 4.5 (3.3-7.6) mg/g. During the follow-up period, 187 men (24%) and 263 women (24.2%) had incident albuminuria and 136 men (17.9%) and 123 women (11.3%) had incident low eGFR. Fifty-four (7.1%) of men and 43 (3.9%) of women had both abnormalities. Among men, higher SHBG was associated with lower risk of low eGFR (pooled hazard ratio [HR] per SD 0.72; 95% CI 0.57, 0.90; p=0.01) and lower risk for CKD (pooled HR per SD 0.70; 95% CI 0.64, 0.95; p=0.01). No significant associations were observed among women.

We conclude that among overweight glucose-intolerant men, higher SHBG was associated with reduced risk of CKD.

Supported By: National Institute of Diabetes and Digestive and Kidney Diseases (U01DK048489)

1574-P
Sex Hormones and Development of Chronic Kidney Disease in the Diabetes Prevention Program Outcomes Study (DPPOS)
CATHERINE KIM, ANA RICARDO, EDWARD J. BOYKO, COSTAS A. CHRISTOPHI,
MARINELLA TEMPROSA, CAROL WATSON, XAVIER PI-SUNYER, RITA R. KALY-
ANI, DPP RESEARCH GROUP, Ann Arbor, MI, Chicago, IL, Seattle, WA, Rockville, MD Los Angeles, CA, New York, NY, Salt Lake City, UT.

Whether endogenous sex hormones are associated with chronic kidney disease (CKD) is not known. We conducted a secondary analysis of longitudinal data from the DPPOS, the follow-up study of the Diabetes Prevention Program (DPP), a randomized trial of diabetes prevention that assigned participants to placebo, metformin, or lifestyle intervention. This analysis included overweight and glucose-intolerant men (n=888) and women (n=1281) not using exogenous sex hormones who had urine albumin-to-creatinine ratio (ACR) > 30 mg/g and normal estimated glomerular filtration ratio (eGFR) > 60 ml/min/1.73 m2.

Sex Hormones (dehydroepiandrosterone (DHEAS), dihydrotestosterone, testosterone, estradiol, estrone, and sex hormone binding globulin (SHBG)) were measured at baseline. CKD was defined as incident low eGFR and/or albuminuria ACR ≥ 30 mg/g. eGFR and ACR were measured annually over 11 years of DPPOS follow-up. Multivariable Cox regression models adjusted for eGFR and log-ACR, age, race/ethnicity, body mass index, blood pressure, insulin resistance, high-density lipoprotein, C-reactive protein, and use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers at baseline. At baseline, the mean (SD) of eGFR was 94 (15) ml/min/1.73 m2, and the median (IQR) of ACR was 4.5 (3.3-7.6) mg/g. During the follow-up period, 187 men (24%) and 263 women (24.2%) had incident albuminuria and 136 men (17.9%) and 123 women (11.3%) had incident low eGFR. Fifty-four (7.1%) of men and 43 (3.9%) of women had both abnormalities. Among men, higher SHBG was associated with lower risk of low eGFR (pooled hazard ratio [HR] per SD 0.72; 95% CI 0.57, 0.90; p=0.01) and lower risk for CKD (pooled HR per SD 0.70; 95% CI 0.64, 0.95; p=0.01). No significant associations were observed among women.

We conclude that among overweight glucose-intolerant men, higher SHBG was associated with reduced risk of CKD.

Supported By: National Institute of Diabetes and Digestive and Kidney Diseases (U01DK048489)
Race and Sex Differences in Diabetic Complications in a Large Health Care System
PING YIN, LUZHENG SHI, ELIZABETH NAUMAN, PETER T. KATZMARZYK, EBONI G. PRICE-HAYWOOD, ALESSANDRA N. BAZZANO, YUN SHEN, GANG HU, Shang- hai, China; New Orleans, LA, Baton Rouge, LA

Existing studies of racial differences in diabetic complications between African Americans and whites have provided conflicting results. The objective of this study was to investigate race and sex differences in diabetic complications between African-American and white patients in Louisiana's largest integrated health delivery system. We performed a prospective cohort study of 28,218 African Americans and 31,237 whites with diabetes. Cox proportional hazard regression was used to estimate the relative risk of each of four health outcomes between African Americans and whites. The age- and sex-adjusted incident rates per 1,000 person-years and 95% confidence intervals (CI) of coronary heart disease (CHD), heart failure, stroke, and end-stage renal disease (ESRD) for African-American patients with diabetes were 59.8 (95% CI 57.7-62.0), 43.5 (41.7-45.4), 34.0 (32.4-35.7), and 56.5 (53.8-59.3), respectively. Compared with African-American patients with diabetes, white patients with diabetes had a higher age- and sex-adjusted incident rate of CHD (63.3 [61.2-65.3]) and lower rates of heart failure (32.0 [30.6-33.4]), stroke (29.7 [28.4-31.1]) and ESRD (45.7 [44.0-47.4]). Men with diabetes had higher age-adjusted incident rates of CHD, heart failure, and ESRD than women with diabetes. Results of the Cox proportional hazard models confirmed racial and sex differences observed in the age- and sex-adjusted incident rates. African American patients with diabetes have higher risks of heart failure, stroke and ESRD than white counterparts, whereas whites with diabetes have a higher risk of CHD than African-American counterparts.

Supported By: Patient-Centered Outcomes Research Institute (C0R1 1396-04884, N0-1509-32527); National Institute of General Medical Sciences (U54GM104940 to G.H.)

1576-P
Insulin Therapy for Insulin Resistant Patients—Harm or Benefit?
CARLOS E. MENDEZ, CHRISTIAN ELER, REBEKAH J. WALKER, LEONARD E. EGEDURE, Milwaukee, WI

Insulin therapy has been proven to be effective in the management of type 2 diabetes. However, in patients with known insulin resistance, additional exogenous insulin used to achieve glycemic control may further contribute to the underlying dysmetabolic process resulting in increased complications. We sought to compare clinical outcomes in patients with diabetes and high insulin resistance by insulin use status. Data from NHANES (2001-2010) was used for this study. Of the 52,195 individuals included in the survey, 1,470 were reported to have diabetes with available serum fasting insulin and glucose levels. Of these, 295 were on insulin. Individuals were categorized to have high or low insulin resistance based on HOMA IR being ≥2 or <2. Receiver operating characteristic (ROC) curve analysis was conducted and positive predictive values (PPV) of available screening tests for CD were evaluated.

Methods: The Gastrointestinal Symptom Scale (GISS) and a Visual Analog Scale (VAS) were used to assess GI symptom type and severity in 2,370 patients with T1D aged 8-45 years as part the screening phase of the Celiac Disease and Diabetes Dietary Intervention and Evaluation Trial (CD-DIET). Co-morbidities, including diabetes-related complications, were extracted from clinical records. The presence and severity of GI symptoms and relationships with demographic, clinical and other diabetes-related factors were evaluated.

Results: Overall, 1386 adults (57.7%) aged 19-45 years and 1002 (42.3%) pediatric patients aged 8-18 years were studied. At least one GI symptom was reported in 34.1% of adults as compared with 21.7% of children (p<0.001). Common symptoms in children included upper abdominal pain, lower abdominal pain and nausea while adults more frequently reported lower GI symptoms with females describing more severe symptoms. Overall, patients with ≥1 GI symptom were more likely to have diabetes complications when adjusted for age and sex (OR=1.14; 95%CI=1.1-1.17; p=0.002). Conversely, patients who reported diabetes complications such as nephropathy, retinopathy and/or cardiovascular disease were 1.94 (95%CI=1.49-2.52) times more likely to report GI symptoms. No association was observed between autoimmune conditions (including screen-detected celiac disease and reported thyroid disease) and GI symptoms.

Conclusions: In this large screening study in a contemporary T1D cohort, significant differences were found between age groups with more frequent GI symptoms in adults. Significant associations were observed between GI symptoms and diabetes complications along with diabetes duration.

Supported By: JDRF

1577-P
Insulin Therapy for Insulin Resistant Patients—Harm or Benefit?
CARLOS E. MENDEZ, CHRISTIAN ELER, REBEKAH J. WALKER, LEONARD E. EGEDURE, Milwaukee, WI

Insulin therapy has been proven to be effective in the management of type 2 diabetes. However, in patients with known insulin resistance, additional exogenous insulin used to achieve glycemic control may further contribute to the underlying dysmetabolic process resulting in increased complications. We sought to compare clinical outcomes in patients with diabetes and high insulin resistance by insulin use status. Data from NHANES (2001-2010) was used for this study. Of the 52,195 individuals included in the survey, 1,470 were reported to have diabetes with available serum fasting insulin and glucose levels. Of these, 295 were on insulin. Individuals were categorized to have high or low insulin resistance based on HOMA IR being ≥2 or <2. Receiver operating characteristic (ROC) curve analysis was conducted and positive predictive values (PPV) of available screening tests for CD were evaluated.

Methods: The Gastrointestinal Symptom Scale (GISS) and a Visual Analog Scale (VAS) were used to assess GI symptom type and severity in 2,370 patients with T1D aged 8-45 years as part the screening phase of the Celiac Disease and Diabetes Dietary Intervention and Evaluation Trial (CD-DIET). Co-morbidities, including diabetes-related complications, were extracted from clinical records. The presence and severity of GI symptoms and relationships with demographic, clinical and other diabetes-related factors were evaluated.

Results: Overall, 1386 adults (57.7%) aged 19-45 years and 1002 (42.3%) pediatric patients aged 8-18 years were studied. At least one GI symptom was reported in 34.1% of adults as compared with 21.7% of children (p<0.001). Common symptoms in children included upper abdominal pain, lower abdominal pain and nausea while adults more frequently reported lower GI symptoms with females describing more severe symptoms. Overall, patients with ≥1 GI symptom were more likely to have diabetes complications when adjusted for age and sex (OR=1.14; 95%CI=1.1-1.17; p=0.002). Conversely, patients who reported diabetes complications such as nephropathy, retinopathy and/or cardiovascular disease were 1.94 (95%CI=1.49-2.52) times more likely to report GI symptoms. No association was observed between autoimmune conditions (including screen-detected celiac disease and reported thyroid disease) and GI symptoms.

Conclusions: In this large screening study in a contemporary T1D cohort, significant differences were found between age groups with more frequent GI symptoms in adults. Significant associations were observed between GI symptoms and diabetes complications along with diabetes duration.

Supported By: JDRF
Results: CL and ELISA data were available for 100/104 and 36/104 patients, respectively. The area under the curve of the ROC for CL TTG was 0.918, while the PPV using the manufacturer referenced upper limit (RUL) of 8 U/ml and reached to 100% at the optimal cut-off determined by our analysis of 57.8 U/ml, which translates to 7.3 times the RUL.

Conclusion: Results from serologic CL and ELISA TTG assays that were greater than 5 times the reported upper limit showed a high PPV for biopsy-confirmed CD in asymptomatic adult and pediatric T1D patients, which may help guide diagnostic evaluation in this population.

Supported By: JDRF Canada

1580-P Diabetes Comorbidity and All-Cause, Cardiovascular, and Cancer Mortality in U.S. Adults
DANJIAJUN SUN, TAO ZHUO, XUANG LI, YORIKO HIEANZA, XIADUN SHANG, VIVIAN FONSECA, LU QI, NEW ORLEANS, LA; MAMERO, LA

Type 2 diabetes is one of the most common chronic diseases in the U.S.; however, few studies have comprehensively assessed the relations between its comorbidities and premature death. Prospective analyses were performed using data linked from National Health Interview Surveys (1997 to 2009) to National Death Index records (2011) among 366,971 adults. Cox models were used to test the relations of diabetes and eleven comorbidities - all-cause, CVD, or cancer mortality. After a median follow-up of 9.8 years (2.9 million person-years), a total of 38,867 participants had died. Compared with common-conditions-free subjects, we ranked hazard ratios (HR [95% CI]) of eleven diabetic comorbidities, and the top three were chronic kidney disease (CKD: 5.3 [4.9-5.7]), liver cirrhosis (5.1 [4.8-5.5]), and blindness (4.4 [3.8-5.1]) for all-cause mortality. Diabetics with CKD (5.9 [5.0-6.9]) and kidney disease (CKD: 5.3 [4.9-5.7]), liver cirrhosis (5.1 [4.6-5.8]), and blindness (2.7 [2.1-3.5]) had an increased risk of cancer mortality (4.1 [3.6-4.6]), whereas CKD and blindness (2.7 [2.1-3.5]) ranked top three for cancer mortality. Diabetes comorbidities may substantially increase the risk of all-cause, CVD, or cancer mortality. Liver disease is more strongly related to cancer mortality, whereas CKD and blindness with CVD. Recognition of these associations may assist with more appropriate and effective screening programs that may help decrease associated mortality.

1582-P Cardiovascular Outcomes and Mortality in Type 2 Diabetes with Associated Cardio-Renal-Metabolic Comorbidities
SUSANNE P, PHILIP B. HUNT, HUNG TA CHEN, SHARON MACLACHLAN, ENRICO REPETTO, JITEN VORA, MIKHAEL KOSIBOROD, Kansas City, MO; WALTHAM, MA; GAITHERSBURG, MD; London, United Kingdom; Liverpool, United Kingdom

Cardio-renal-metabolic comorbidities (CRMCs) associated with type 2 diabetes (T2DM) increase patient morbidity and mortality. We evaluated the incremental contribution of various CRMCs to the risk of myocardial infarction, stroke, or cardiovascular death (MACE), heart failure (HF), and all-cause mortality (ACM) in patients with newly diagnosed T2DM. Using ICD-9 codes, T2DM patients were identified in a U.S. EMR (Humedica/Optum) database along with other CRMCs (hypertension [HTN], hyperlipidemia [HPLD], chronic kidney disease [CKD]) at the time of T2DM diagnosis. Patients’ records were assessed for the occurrence of MACE, HF, and ACM. Between 1 Jan 2011 and 31 Mar 2015, 180722 incident T2DM patients were identified (age, mean [SD]): 62.4 [13.5], 52.0% male with/without CRMCs. T2DM only (n=25114, 13.9%), T2DM+HTN (n=20683, 11.5%), T2DM+HPLD (n=13274, 7.3%); T2DM+HTN+HPLD (n=52415, 29.0%), and T2DM+HTN+HPLD+CKD (9.9%). The risk of MACE, HF and ACM increased with a greater number of CRMCs (Table). CKD being associated with the highest incremental risk for ACM. In patients with new diagnosis of T2DM, the risk of MACE, HF, and death increased incrementally with a greater number of CRMCs; with CKD being the main driver of mortality. These results may have implications for risk factor management, and potentially selection of treatment strategies among T2DM patients with various CRMCs.

Table. MACE, HF, and ACM Rates in Patients with Incident T2DM and Cardio-Renal-Metabolic Diseases

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>CRMCs at time of T2DM Diagnosis</th>
<th>Event rate (% 95% CI) events/100 PY</th>
<th>Incremental % increase in relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>T2DM only</td>
<td>5.16 (5.00, 5.32)</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>T2DM + HTN + HPLD</td>
<td>7.04 (6.91, 7.18)</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>T2DM + HTN + HPLD + CKD</td>
<td>9.15 (8.87, 9.43)</td>
<td>30</td>
</tr>
<tr>
<td>HF</td>
<td>T2DM only</td>
<td>4.84 (4.69, 5.00)</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>T2DM + HTN + HPLD</td>
<td>6.24 (6.12, 6.37)</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>T2DM + HTN + HPLD + CKD</td>
<td>8.40 (8.14, 8.66)</td>
<td>35</td>
</tr>
<tr>
<td>ACM</td>
<td>T2DM only</td>
<td>2.26 (2.16, 2.37)</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>T2DM + HTN + HPLD</td>
<td>2.57 (2.50, 2.64)</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>T2DM + HTN + HPLD + CKD</td>
<td>5.19 (5.01, 5.38)</td>
<td>102</td>
</tr>
</tbody>
</table>

MACE, all-cause mortality; CI, confidence interval; CRMCs, cardio-renal-metabolic comorbidities; CKD, chronic kidney disease; HF, heart failure; HTN, hypertension; HPLD, hyperlipidemia; MACE, myocardial infarction, stroke, or cardiovascular death; PY, patient-years; T2DM, type 2 diabetes mellitus.
Epidemiology—Diabetes Complications

1583-P

No Improvement in Glycemic Control or Rates of Diabetes-Related Complications for People with Type 2 Diabetes—Results from 10 Years of the International Diabetes Management Practices Study (IDMPS)

Yigit K. Shenher, Juan J. Gagliardino, Hasan M. Ikiova, Fernando J. Lavelle-Gonzalez, Ambady Ramachandran, Ghaida Kaddaha, Jean Claude Mbanya, Marina V. Shestakova, Jean-Marc Chantelot, Juliana C. Chan, Bogota, Colombia; La Plata, Argentina; Istanbul, Turkey; Montreux, Mexico; Chennai, India; Dubai, United Arab Emirates; Yaoundé, Cameroon; Moscow, Russian Federation; Paris, France; Hong Kong, China

Diabetes treatment has evolved over the last decade. During this time, the IDMPS, a global observational survey on the management and patterns of care of people with type 1 and type 2 (T2D) diabetes in the developing world, has collected data in 7 individual waves. Each wave enrolled different participants. We report the glycemic condition and the frequency of diabetes-related cardiovascular complications in participants with T2D observed between 2005 and 2017 in 48 countries across Africa, the Middle East, South Asia, Latin America, Asia, and Eurasia.

From Wave 1 to Wave 7, no improvement in the proportion of people achieving HbA1c <7% was seen. This is the case for all groups, i.e., those receiving oral glucose-lowering drugs (OGLDs) plus injectable treatments, and those receiving insulin (Table). The proportions of participants with micro- and macrovascular complications appear relatively unchanged. Throughout all waves, the proportion of participants receiving insulin remained constant (≈25%). For those treated with OGLDs plus basal insulin, the median daily dose of insulin was 0.21 U/kg in 2005 and 0.32 U/kg in 2017; over the same period, the median BMI at diagnosis increased from 26 kg/m² to 29 kg/m². This lack of progress highlights the continued need for improvements in diabetes management and education.

Table. Achievement of HbA1c <7% and incidence of micro- and macrovascular complications in people with T2D enrolled in IDMPS

<table>
<thead>
<tr>
<th>T2D</th>
<th>OGLDs</th>
<th>Wave 1</th>
<th>Wave 2</th>
<th>Wave 3</th>
<th>Wave 4</th>
<th>Wave 5</th>
<th>Wave 6</th>
<th>Wave 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>393</td>
<td>0.35</td>
<td>0.32</td>
<td>0.31</td>
<td>0.30</td>
<td>0.29</td>
<td>0.29</td>
<td>0.29</td>
</tr>
<tr>
<td>Age (mean, years)</td>
<td>55.9</td>
<td>51.8</td>
<td>51.8</td>
<td>51.9</td>
<td>51.3</td>
<td>50.7</td>
<td>51.1</td>
<td>51.9</td>
</tr>
<tr>
<td>Diabetes duration (mean, years)</td>
<td>7.1</td>
<td>6.9</td>
<td>7.1</td>
<td>6.8</td>
<td>6.7</td>
<td>6.7</td>
<td>6.7</td>
<td>7.0</td>
</tr>
<tr>
<td>HbA1c (mean, %)</td>
<td>7.5</td>
<td>7.6</td>
<td>7.5</td>
<td>7.5</td>
<td>7.6</td>
<td>7.9</td>
<td>7.6</td>
<td>7.6</td>
</tr>
<tr>
<td>HbA1c &lt;7%, %</td>
<td>48.0</td>
<td>46.7</td>
<td>45.6</td>
<td>48.5</td>
<td>45.1</td>
<td>42.0</td>
<td>44.7</td>
<td>44.7</td>
</tr>
<tr>
<td>Spinal BP (mmHg, mean)</td>
<td>120.6</td>
<td>122.2</td>
<td>122.9</td>
<td>126.8</td>
<td>131.6</td>
<td>132.5</td>
<td>128.0</td>
<td>129.0</td>
</tr>
<tr>
<td>Diabetic BP (mmHg, mean)</td>
<td>178.6</td>
<td>179.2</td>
<td>177.5</td>
<td>174.6</td>
<td>179.7</td>
<td>169.7</td>
<td>176.1</td>
<td>176.7</td>
</tr>
<tr>
<td>Total serum cholesterol (mmol/L)</td>
<td>5.07</td>
<td>191.3</td>
<td>180.0</td>
<td>190.3</td>
<td>189.0</td>
<td>190.2</td>
<td>188.9</td>
<td>189.9</td>
</tr>
<tr>
<td>15 mmol/L and above, %</td>
<td>40.6</td>
<td>39.7</td>
<td>34.6</td>
<td>27.1</td>
<td>30.9</td>
<td>36.4</td>
<td>31.9</td>
<td>31.5</td>
</tr>
<tr>
<td>15-17 mmol/L and above, %</td>
<td>20.7</td>
<td>18.5</td>
<td>14.7</td>
<td>13.8</td>
<td>13.3</td>
<td>13.3</td>
<td>8.6</td>
<td>8.6</td>
</tr>
<tr>
<td>T2D with OGLDs</td>
<td>Wave 1</td>
<td>Wave 2</td>
<td>Wave 3</td>
<td>Wave 4</td>
<td>Wave 5</td>
<td>Wave 6</td>
<td>Wave 7</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>393</td>
<td>0.35</td>
<td>0.32</td>
<td>0.31</td>
<td>0.30</td>
<td>0.29</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>Age (mean, years)</td>
<td>55.9</td>
<td>51.8</td>
<td>51.8</td>
<td>51.9</td>
<td>51.3</td>
<td>50.7</td>
<td>51.1</td>
<td>51.9</td>
</tr>
<tr>
<td>Diabetes duration (mean, years)</td>
<td>7.1</td>
<td>6.9</td>
<td>7.1</td>
<td>6.8</td>
<td>6.7</td>
<td>6.7</td>
<td>6.7</td>
<td>7.0</td>
</tr>
<tr>
<td>HbA1c (mean, %)</td>
<td>7.5</td>
<td>7.6</td>
<td>7.5</td>
<td>7.5</td>
<td>7.6</td>
<td>7.9</td>
<td>7.6</td>
<td>7.6</td>
</tr>
<tr>
<td>HbA1c &lt;7%, %</td>
<td>48.0</td>
<td>46.7</td>
<td>45.6</td>
<td>48.5</td>
<td>45.1</td>
<td>42.0</td>
<td>44.7</td>
<td>44.7</td>
</tr>
<tr>
<td>Spinal BP (mmHg, mean)</td>
<td>120.6</td>
<td>122.2</td>
<td>122.9</td>
<td>126.8</td>
<td>131.6</td>
<td>132.5</td>
<td>128.0</td>
<td>129.0</td>
</tr>
<tr>
<td>Diabetic BP (mmHg, mean)</td>
<td>178.6</td>
<td>179.2</td>
<td>177.5</td>
<td>174.6</td>
<td>179.7</td>
<td>169.7</td>
<td>176.1</td>
<td>176.7</td>
</tr>
<tr>
<td>Total serum cholesterol (mmol/L)</td>
<td>5.07</td>
<td>191.3</td>
<td>180.0</td>
<td>190.3</td>
<td>189.0</td>
<td>190.2</td>
<td>188.9</td>
<td>189.9</td>
</tr>
<tr>
<td>15 mmol/L and above, %</td>
<td>40.6</td>
<td>39.7</td>
<td>34.6</td>
<td>27.1</td>
<td>30.9</td>
<td>36.4</td>
<td>31.9</td>
<td>31.5</td>
</tr>
</tbody>
</table>

1584-P

Frequency of Diabetes-Related Complications in Type 1 and Type 2 Diabetes—Results from the International Diabetes Management Practices Study (IDMPS)

Juan J. Gagliardino, Pablo Aschner, Hasan M. Ikiova, Fernando J. Lavelle-Gonzalez, SR., Ambady Ramachandran, Ghaida Kaddaha, Jean Claude Mbanya, Marina V. Shestakova, Jean-Marc Chantelot, Juliana C. Chan, Bogota, Argentina; Colombia; La Plata, Argentina; Istanbul, Turkey; Montreux, Mexico; Chennai, India; Dubai, United Arab Emirates; Yaoundé, Cameroon; Moscow, Russian Federation; Paris, France; Hong Kong, China

Complications associated with diabetes have a considerable negative impact on patient wellbeing and economic contribution, and place a large burden on healthcare and welfare systems. Annual screening for diabetes-related complications is recommended in treatment guidelines. The IDMPS is a global observational survey on the management and patterns of care of people with type 1 (T1D) and type 2 (T2D) diabetes in the developing world. We report details of the burden of the disease in 2016–17 in 24 countries across Africa, the Middle East, South Asia, and Eurasia. Physician-reported annual screening rates for diabetes-related complications of the eye (retina examination), nerve (monofilament test), kidney (blood or urine test), foot (ulcer examination), blood pressure (SBP/DBP), and metabolism (lipid profile test) ranged from 62.5%–94.3% (Table). High rates of complications were recorded (independent of screening); microvascular complications (eye, nervous system, and kidney) were reported in almost 50% of people with T1D or T2D; macrovascular complications (heart conditions and stroke) were reported in 5.9% and 16.0% of people, respectively. Screening for diabetes-related complications in the developing world is not universal. Dedication of more resources to screening may reduce the rates of development or worsening of complications.

Table.

<table>
<thead>
<tr>
<th>Time since diagnosis (mean, years)</th>
<th>HbA1c (mean, %)</th>
<th>People with HbA1c &lt;7%, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1D N=2600</td>
<td>13.1</td>
<td>8.4</td>
</tr>
<tr>
<td>T2D N=303</td>
<td>9.8</td>
<td>8.1</td>
</tr>
<tr>
<td>People screened in the previous year, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye</td>
<td>Nervous system</td>
<td>Kidney</td>
</tr>
<tr>
<td>T1D N=2600</td>
<td>69.0</td>
<td>61.7</td>
</tr>
<tr>
<td>T2D N=303</td>
<td>67.0</td>
<td>62.5</td>
</tr>
</tbody>
</table>

| People who reported history of complications, % | | |
| Eye | Nervous system | Kidney | Heart | Stroke | Microvascular | Macrovascular |
| T1D N=2600 | 35.9 | 35.3 | 22.3 | 4.2 | 4.8 | 47.7 | 5.9 |
| T2D N=303 | 30.0 | 36.4 | 19.7 | 15.3 | 2.6 | 48.4 | 16.0 |

Supported By: Sanofi

1585-P

Protection from Severe Periodontal Disease among People with Type 1 Diabetes with Duration of 50 Years or Longer

Takorni Shinjio, Atsushi Ishikado, Hatice Hasturk, Liane J. Tinsley, David M. Pober, I-Hsien Wu, Thomas E. Van Dyke, Robert J. Genco, George L. King, Boston, MA; Takatsuki, Japan; Cambridge, MA; Buffalo, NY

Periodontal disease (PD) is more common and severe in people with diabetes than the general population. The presence of severe PD is correlated with decreased survival, since it can potentially affect glycemic control and severity of complications in people with diabetes. We have reported that Medalists (people with T1DM of 50 years or longer duration) may have endogenous protective factors for the development of diabetic nephropathy (DN) and retinopathy (DR). This study assessed the prevalence of PD in the Medalist cohort and correlated it to the known risk factors of PD and diabetic complications. Severity of PD was defined in a subset (n=170) of Medalists with comparable characteristics of the whole cohort, according to the AAP criteria. The prevalence of severe PD was dramatically decreased in Medalists (13.5%) compared with other studies of people with diabetes of similar age, approximately 33%. Clinical parameters, such as male gender, chronological age, age at diagnosis, and total insulin dose were correlated positively with severity of PD (p=0.04, 0.01, 0.03, and 0.02, respectively).

Supported By: Sanofi
while duration of disease, hemoglobin A1c, BMI, and lipid profiles did not exhibit any correlation. Interestingly, detectable plasma C-peptide levels correlated inversely with severity of PD (p=0.04). Systemic inflammatory markers, such as plasma IL-6, clearly correlated positively with the severity of PD (p=0.01). Serum antibody titer against Porphyromonas gingivalis (Pg), a known pathogen of PD, trended with severity of PD (p=0.08). Amongst the various complications, only the prevalence of CVD correlated positively with severity of PD (p=0.02). These results suggest that Medalists are protected from severe PD even with hyperglycemia. The endogenerative protective factors for PD could be similar to those for CVD, possibly related to endogenous produced insulin to neutralize the chronic inflammation caused by residual infection with Pg in the gingival tissues.

Supported By: National Institutes of Health

1586-P

Projections of Prevalence of Diabetes With and Without CKD in Southwestern American-Indians

MEDIA E. PAVKOV, ANNIKA HOYER, EDWARD W. GREGG, RALPH BRINKS, PETER H. BENNETT, ATLANTA, GA; DÜSSELDORF, GERMANY; PHOENIX, AZ

The combination of high diabetes prevalence, declining mortality trends and high chronic kidney disease (CKD) prevalence has raised concerns about the future burden of CKD in the American Indian population. We modeled the future prevalence of diabetes and CKD in a Southwestern American Indian population well-characterized for type 2 diabetes using data from research examinations conducted on 4,476 participants between 1995 and 2007. Diabetes was assessed by 2-hour glucose tolerance testing. CKD was defined by estimated GFR (eGFR) <60 ml/min/1.72 m². Estimates of age-specific prevalence of diabetes without CKD (p1) and with CKD (p2) were projected through 2030, using illness-death models of the observed prevalence, incidence and death rates for men and women (Figure). For women 40 years old, p1 is projected to decline from 42.2% in 2010 to 17.1% in 2030, whereas p2 is projected to increase from 3.3% to 34.9% in the same decades. Among 40-year-old men, p1 is projected to decline from 42.3% in 2010 to 29.8% in 2030, concurrent with an increase in p2 from 3.4% in 2010 to 8.2% in 2030. Similar trends were observed for older ages, whereas for those younger than 40 years, the increase in p2 was most prominent among women.

In conclusion, the model provides assessment of the future burden of diabetes and diabetes-related CKD, projecting a marked increase in the proportion of people with diabetes who will have CKD over the next two decades.

Figure. Projected trends in prevalence of type 2 diabetes without CKD (p1) and with CKD (p2) in women (upper panels) and men (lower panels).

1587-P

Characteristics and Mortality of Recurrent Diabetic Ketoacidosis (DKA) in Adults and Children with Type 1 Diabetes (T1D)

PRIYATHAMA VELU, JULIAN FONG, NNL DHRUV, CLEMENTINA RAMOS, J. SONYA HAW, RODOLFO J. GALINDO, GEORGIA DAVIS, MAYA PAVYMAN, FRANCISCO J. PASQUEL, GUILLERMO E. UMPIERREZ, ATLANTA, GA

Recurrent DKA is associated with increased mortality in children; however, data is limited in adults. We compared clinical characteristics and outcomes of adults (>18 years) and children (<18 years) at enrollment with recurrent DKA (>1 episode) within the T1D Exchange clinic registry (n=1193). DKA episodes were self-reported as those experienced 12 months prior to enrollment and before each study visit.

We identified 1758 people with recurrent DKA after diagnosis (Table). Median follow-up was 3.6 years. Adults with recurrent DKA had more islet cell or pancreatic transplant, less insurance and higher mortality compared to children, but less DKA at diagnosis. In both children and adults, mortality was higher with age (children: OR 1.24, 95% CI 1.02,1.50; adults: OR 1.09, 95% CI 1.06, 1.11) and no insurance (children: OR 3.83, 95% CI 1.32, 11.09; adults: OR 2.29, 95% CI 1.12, 4.69). Children with recurrent DKA had higher mortality (OR: 4.21, 95% CI 1.28, 13.86) compared to adults (OR: 2.36, 95% CI 0.53, 10.46). DKA at diagnosis of T1D was associated with higher mortality in adults (OR: 2.97, 95% CI 1.44, 6.11) but not in children (OR: 1.40, 95% CI 0.49, 3.97).

Adults and children with recurrent DKA have poor control but differ in socioeconomic factors and presentation of T1D. Even though adults present less with DKA at diagnosis, presentation with DKA is associated with higher mortality.

Table.

1588-P

Glycemic Control and Infections among U.S. Hemodialysis Patients with Diabetes Mellitus

JINNIE J. RHEE, YUANCHAI ZHENG, MARIA MONTEZ-RATH, WOLFGANG WINKELMAYER, PALO ALTO, CA; HOUSTON, TX

Patients with diabetes mellitus (DM) and those who are on hemodialysis (HD) may be particularly vulnerable to infections, but there is a dearth of clinical data on the relationship between glycemic control and infections in patients with DM on HD. We used data from the U.S. Renal Data System and the electronic health records from a large U.S. dialysis provider (DaVita, Inc.) merged at the patient level. We included adult Medicare-insured patients with DM aged ≥18 years who initiated in-center maintenance HD treatment from 2006 to 2011 and survived >90 days. The exposure was time-averaged HbA1c and quarterly mean HbA1c values were categorized as follows: <5.5% (reference), 5.5–<6.5%, 6.5–<7.5%, 7.5–<8.5%, and ≥8.5%. We used Medicare claims to ascertain infection-related hospitalizations and the ESRD Death Notification (CMS-2746) to identify death from infections. The primary outcome was the composite of infection-related death or hospitalization with all-cause death and transplant treated as competing risks using the Kaplan-Meier multiple imputation (MI) method. Missing data was handled through MI. We used extended-Cox models to estimate multivariable-adjusted hazard ratios (HR) and 95% CI for the associations between time-averaged HbA1c and the outcome, adjusting for baseline demographics and quarterly updated comorbidities from claims, central venous catheter use, and time-averaged vital signs and laboratory results. Among 33,753 eligible patients, 9415 infection-related hospitalizations occurred and 605 deaths were linked to infection. Compared with patients with HbA1c ≥8.5%, the adjusted HRs for infection-related death or hospitalization were 1.03 (CI, 0.96, 1.09), 1.02 (CI, 0.97, 1.09), 1.02 (CI, 0.95, 1.09), and 1.02 (CI, 0.95, 1.09) for patients with HbA1c <5.5%, 5.5–<6.5% (reference), 6.5–<7.5%, 7.5–<8.5%, and ≥8.5%, respectively (p-trend=0.97).

In summary, time-averaged HbA1c was not associated with the risk of a composite outcome of infection-related mortality or hospitalization.

Supported By: National Institute of Diabetes and Digestive and Kidney Diseases (F22DK103473)

1589-P

The Impact of Sarcopenia and Diabetes on Postoperative Complications in Abdominal Surgery Patients

GEORGINA DAVIS, MAYA PAVYMAN, ADAMINGER, MONICA UMPIERREZ, APRANNA KAKARALA, LIMIN PENG, SHAILESH NAIR, FRANCISCO J. PASQUEL, GUILLERMO E. UMPIERREZ, ATLANTA, GA

Sarcopenia and diabetes (DM) are independent predictors of poor postoperative outcomes. Limited data exists on the prevalence and impact of

ADA-Supported Research  Moderated Poster Discussion
both conditions on perioperative outcomes in abdominal surgery patients. We performed a retrospective analysis of patients undergoing abdominal surgery who had abdominal CT imaging within 30 days prior to surgery. Measurements of psoas muscle surface area and attenuation values (in Hounsfield units) were recorded at the most anterior convex part of the lumbar spine corresponding to the level of the L3/L4 vertebrae. Sarcopenia was defined as the lowest sex-specific quartile of psoas muscle density. Composite of complications was determined using ICD-9 coding and included: acute MI, stroke, wound infection, pneumonia, UTI, bacteremia and respiratory failure. Among 343 patients, 85 (24%) met criteria for sarcopenia. Patients with sarcopenia were older, more likely to be caucasian, had a longer length of hospital stay and had more postoperative complications. In fully adjusted analyses, patients with both DM and sarcopenia had four-fold higher rates of complications compared to those without DM or sarcopenia (Table).

In summary, sarcopenia is associated with higher rates of complications in patients with and without DM; the combination of sarcopenia and DM confers an additional risk of perioperative complications in patients undergoing abdominal surgery.

### Table.

<table>
<thead>
<tr>
<th></th>
<th>No Sarcopenia (n=258)</th>
<th>Sarcopenia (n=85)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>56.7 ± 15.27</td>
<td>63.5 ± 14.29</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.3 ± 6.68</td>
<td>27.2 ± 7.03</td>
<td>0.64</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>119 (46)</td>
<td>39 (46)</td>
<td>0.97</td>
</tr>
<tr>
<td>Caucasian</td>
<td>154 (60)</td>
<td>66 (78)</td>
<td>0.005</td>
</tr>
<tr>
<td>African American</td>
<td>82 (32)</td>
<td>16 (21)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>20 (8)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Diabetes status, n (%)</td>
<td></td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>No diabetes</td>
<td>202 (78)</td>
<td>58 (69)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>56 (22)</td>
<td>27 (32)</td>
<td></td>
</tr>
<tr>
<td>LOS, median, days</td>
<td>9 (6, 17)</td>
<td>15 (10, 21)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

**Odds ratio* of composite of complication adjusted for age, gender, BMI and race.**

*Supported By: Jacobs Family Foundation

**1590-P**

Prospective Study on Incidence of Cardiovascular-Renal Diseases, Severe Hypoglycaemia, and Death in Chinese with Latent Autoimmune Diabetes in Adults

**ANDREA LUK, ERIC S. LAU, CADMON K.P. LIM, ELAINE CHOW, RONALD C. MA, ALICE F. KONG, JULIANA C. CHAN, Hong Kong, China**

**Objectives:** Few studies have examined the progression to chronic complications in patients with latent autoimmune diabetes in adults (LADA). We compared incidence of cardiovascular-renal diseases, severe hypoglycaemia and death in patients with LADA and type 2 diabetes.

**Methods:** Between 1995-2012, 1569 Chinese with young-onset (age of diagnosis <40 years) non-type 1 diabetes underwent comprehensive diabetes assessment at Prince of Wales Hospital, Hong Kong. LADA (n=124 (7.9%)) was identified by positive anti-glutamic acid decarboxylase antibodies measured from stored serum. Patients were followed for new events of cardiovascular disease (CVD), end-stage renal disease (ESRD), severe hypoglycaemia and all-cause death until June 2017.

**Results:** At baseline, patients with LADA (mean age: 43.4 years, median diabetes duration: 6.0 years) had lower serum C-peptide, BMI and triglyceride but higher HbA1c than patients with type 2 diabetes (mean age: 41.7 years, median diabetes duration: 8.0 years). Use of insulin was more frequent in those with LADA whilst use of non-insulin glucose lowering drugs was comparable. Over follow-up period of 10 years, incidence (in 1000 person-year) of CVD, ESRD, severe hypoglycaemia and death were 4.1, 8.0, 20.2 and 5.5 in LADA, and 10.4, 9.5, 10.8 and 8.9 in type 2 diabetes, respectively. Using Cox regression, patients with LADA had lower hazard to have CVD (hazard ratio [HR] 0.41 [95% CI 0.19-0.90], p=0.024), higher hazard to have severe hypoglycaemia (HR 1.74 [95% CI 1.15-2.62], p=0.008) and similar risks for ESRD and mortality compared with type 2 diabetes, adjusted for age, gender, disease duration, smoking, glycaemic and metabolic indices, and baseline insulin use.

**Conclusions:** Patients with LADA had lower risks of CVD but higher risks of severe hypoglycaemia than type 2 diabetes.

**Supported By:** Hong Kong Research Grants Council (14120215). Hong Kong Theme-Based Research Scheme (T12-402/13N)

**1591-P**

Cutaneous Reactions to Continuous Glucose Monitoring and Continuous Subcutaneous Insulin Infusion Devices in Type 1 Diabetes

**RACHEL K. SEVERIN, RACHELLE GANDICA, LAURA E. LEVIN, DONALD V. BEL-SITO, MARIA C. GARZON, KRISTEN M. WILLIAMS, New York, NY**

Continuous glucose monitoring (CGM) and continuous subcutaneous insulin infusion (CSII) are the standard of care for type 1 diabetes (T1D). There is little reported on skin complications related to these devices. This study documents cutaneous reactions to CGM and CSII devices in children and young adults with T1D.

121 subjects (3-25 years) with T1D and CGM and/or CSII use were recruited over a 3-month period from the Naomi Berrie Diabetes Center at Columbia University Medical Center. A 5-question survey was completed for each subject detailing demographic data and device-related skin problems. 60% of subjects reported skin problems related to CGM and/or CSII use. Terms most frequently used to describe their reactions were red, itchy, painful, and rash. Subjects who used both CGM and CSII were more likely to report skin problems than those who used only CSII (OR [2.8]; p=0.015; 95% CI [1.2, 6.7]). There were no associations between skin problems and age, sex, or race/ethnicity.

22% of subjects with an adverse skin event discontinued use of their device due to their skin problem. 7% were evaluated by a dermatologist. 81% used a range of products to treat their symptoms, with variable perceived clinical effects.

Skin complications related to CSII or CGM devices are common, and may lead to interruption or discontinuation of treatment. Future studies to elucidate the causes are needed.

**Table 1. Supplemental Products Used by Patients: Effects on Skin Problems.**

<table>
<thead>
<tr>
<th>Product category</th>
<th>Patients reporting clinical worsening (%)</th>
<th>Patients reporting no change (%)</th>
<th>Patients reporting improvement (%)</th>
<th>Patients reporting discordant effects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adhesive barrier wipe</td>
<td>27% (10/37)</td>
<td>48% (13/27)</td>
<td>11% (3/27)</td>
<td>15% (4/27)</td>
</tr>
<tr>
<td>Transparent film dressing</td>
<td>27% (10/37)</td>
<td>48% (13/27)</td>
<td>11% (3/27)</td>
<td>7% (2/27)</td>
</tr>
<tr>
<td>Topical steroid</td>
<td>22% (7/32)</td>
<td>18% (6/22)</td>
<td>0% (0/22)</td>
<td>5% (1/22)</td>
</tr>
<tr>
<td>Hydrocolloid adhesive pad</td>
<td>13% (8/63)</td>
<td>15% (9/63)</td>
<td>15% (9/63)</td>
<td>0% (0/13)</td>
</tr>
<tr>
<td>Topical antibiotic</td>
<td>11% (6/56)</td>
<td>18% (10/56)</td>
<td>0% (0/11)</td>
<td>0% (0/11)</td>
</tr>
<tr>
<td>Adhesive remover</td>
<td>10% (5/50)</td>
<td>40% (4/10)</td>
<td>10% (1/10)</td>
<td>0% (0/10)</td>
</tr>
</tbody>
</table>

**Supported By:** Jacobs Family Foundation

**1592-P**

Impact of Glycaemic Control on Bone Metabolism in Adult Patients with Type 1 Diabetes Mellitus

**ELEFTHERIA BARMPA, MARIANNA VLYCHOU, STELIDOS TIGAS, GEORGE N. KOKOULOS, ALEXANDRA BARGIDITA, Laurus, Greece, Ioanna, Greece, Athens, Greece**

**Introduction:** Type 1 diabetes mellitus (T1DM) is associated with reduced bone mineral density (BMD), increased bone turnover and impaired bone microarchitecture. However, data regarding the influence of glycaemic control on bone metabolism are limited. The aim of this study was to evaluate BMD and bone remodeling markers in patients with T1DM in relation to changes in glycaemic control.

**Methods/Design:** We studied 118 patients with T1DM and age 20-50 years (mean 34.6±9.7 years, M/F:53/65), diabetes duration >5 years and no diabetic complications and 95 healthy controls matched for age, sex and body mass index (BMI). All T1DM participants were re-examined after one year (FU). In both groups, measurements of glycated hemoglobin (HbA1c) and BMD at lumbar spine (LS) and femoral neck (FN) by dual energy X-ray absorptiometry (DXA) were performed. Bone resorption and formation was assessed by measurements of C -crosslaps and of type 1 procollagen total N-terminal propeptide (PINP) in serum. Currently, seventy T1DM patients completed the FU and had repeat biochemical and BMD measurements. Based on current literature, BMD changes of ≥3% at the LS and of ≥5% at the FN were considered significant.

**Supported By:** Jacobs Family Foundation

**ADA-Supported Research**
Results: In the T1DM group, mean duration of the disease was 15.8±2.6 years and mean HbA1c was 8.1±1.4%. Subject in the T1DM group had lower BMD and Z-score at LS and FN compared to those in the control group (LS: p=0.038, p=0.02) (FN: p=0.041, p=0.038). At baseline, no significant differences in β-crosslaps and TP1NP were observed between the two groups. Out of the 70 T1DM patient who have completed FU so far, 42/70 patients had ≥0.5% reduction in HbA1c, 12/70 had about the same HbA1c (+0.4%) and 16/70 had ≥0.5% increase in HbA1c. In the 42 patients with improved HbA1c, BMD increased by 3.4% at the LS and by 5.7% at the FN, and TP1NP was significantly higher compared to baseline (p=0.043).

Conclusion: T1DM is associated with reduced BMD but improvement of glycaemic control appears to ameliorate BMD and bone turnover.

EPIDEMIOLOGY—DIABETES COMPLICATIONS

Racial Variation in the Relationship of Diabetes with Pancreatic Cancer Risk

DAMIYAH CONWAY, WILLIAM J. BLOT, Tyler, TX; Nashville, TN

Pancreatic cancer is one of the most fatal malignancies, with a 5-year survival of ~8% and is the 4th leading cause of cancer death. It is also one of the cancers most tightly linked to diabetes even when recent diabetes diagnosis and reverse causation are ruled out. The highest rates of pancreatic cancer are found among blacks in the U.S., yet despite nearly twice the prevalence of diabetes among blacks compared to whites, as well as blacks’ increased prevalence of obesity, another key risk factor, little is known about the interrelationship between diabetes and pancreatic cancer among blacks and whether this accounts for the observed racial disparity. We tested the relationship of diabetes with the incidence of pancreatic cancer and whether this relationship varied between blacks and whites. Our null hypothesis was that diabetes would not differentially risk among blacks compared to whites. Using the Southern Community Cohort Study, we conducted a cancer follow-up (2002-2015) of a cohort of mostly low income black and white participants aged 40-79 with (n=17,644) and without diabetes (n=64,870) at cohort entry. Mean age and diabetes duration of those with diabetes was 59.0 and 9.5 years, respectively. Mean age of those without diabetes was 51.8 years. Logistic regression was used. A total of 507 incident cases of pancreatic cancer were observed. In analysis controlling for age, sex, race, current and former smoking, and BMI, diabetes was a significant risk factor for pancreatic cancer (OR=1.48, 95% CI: 1.13-2.94). In race-stratified analyses, the increases associated with diabetes were seen among both blacks (OR=1.46, 95% CI=1.06-2.02) and whites (OR=1.60, 95% CI=0.95-2.67). After control for diabetes, the black excess in risk of pancreatic cancer was attenuated (OR=1.25, 95% CI=0.96-1.64). The findings suggest that diabetes affects pancreas cancer risk regardless of race, but that the higher prevalence of diabetes among blacks contributes to their elevated risk of pancreatic cancer.

Supported By: National Institutes of Health; National Cancer Institute

Altered Neural Dynamics during a Flanker Attention Task in Patients with Type 1 Diabetes

CHRISTINE M. EMBURY, TIMOTHY J. MCDERMOTT, ALEX J. WEISMANN, KAITLIN BRAU, CYRUS DESOUZA, ANDJELA DRINIC, TONY W. WILSON, Omaha, NE

Background: Patients with type 1 diabetes appear to have deficits in specific cognitive domains, particularly in attention and executive function (1). In this study, we used magnetencephalography (MEG, 2), a noninvasive functional neuroimaging method, to identify neuronal changes in attention processing in otherwise healthy young adults with type 1 diabetes during euglycemia.

Methods: Adults with type 1 diabetes and no micro- or macro-vascular complications (N = 38) completed a visual selective attention task during MEG. A demographically-matched control group without type 1 diabetes was used for comparison. Each trial began with a fixation cross presented centrally, followed by a row of 5 arrows. Participants were asked to respond regarding the direction of the middle arrow (right index finger for left, right middle finger for right) and ignore the flanking arrows that were presented in either blocks and conditions or no block (condition). All MEG data was processed following standard protocols (3), and the resulting images of functional brain activity were examined statistically.

Results: While no differences in reaction time or accuracy were found between groups, patients recruited a more widespread network of task relevant brain regions compared to controls, particularly the prefrontal cortex and anterior cingulate. Patients had a greater alpha increase from baseline in the anterior cingulate (p < .01), an important brain region in attention, and in the prefrontal cortex (p < .01) as compared to controls, likely reflecting compensatory mechanisms at play.

Supported By: National Institutes of Health, National Cancer Institute

Using Google Cloud and Predictive Analytics to Promote Influenza Vaccination among People with Diabetes

JAN LUSKA, AASHIMA GUPTA, ANGUS THOMSON, SANDRINE I. SAMSON, HENRY G. MILLS, SR., MICHAEL E. GREENBERG, MILIND KAMKOLKAR, ANNE C. BEAL, MARYSE BEAUDIN, Paris, France, Lafayette, CA; Lyon, France, Swiftwater, PA; Bridgewater, NJ; Cambridge, MA

Background: Although influenza vaccination is recommended for people with type 1 and 2 diabetes, uptake is suboptimal, often leading to complications and hospitalizations. Vaccine acceptance is influenced by several psychosocial and behavioral factors, including one’s knowledge of flu and vaccination beliefs. We used novel data sources to understand predictors of vaccination adherence among countries and subpopulations.

Methods: We used VaxxTrends, a proprietary dataset, to identify variables influencing vaccine uptake among adults in the U.S., China, France, Mexico, and U.K. We combined the data with NHI Interview Survey results, which offer insights into health behaviors of Americans with diabetes. This information was aggregated with data from Google’s FluTrend, which signals flu incidence, and Google Trends Application Programming Interface, which tracks search keyword popularity by location and date in a de-identified fashion. Cluster analyses indicated factors most positively and negatively associated with acceptance and adherence.

Results: Our analysis indicates that targeted interventions focusing on country-specific drivers of flu vaccination adherence among subpopulations of people with diabetes could lead to an increase in vaccination rates of up to 5%. In France, Mexico and U.K., relationships with HCPs were most predictive of vaccination adherence, while in the U.S., reminders and strategies addressing affordability concerns were key predictors. In China, encouragement from relatives, convenient options for receiving vaccinations and education to counter fear of flu vaccination may have the greatest impact. Within countries, we found some patient subgroups were more amenable to vaccination than others.

Conclusion: By identifying country-specific behavioral drivers of flu vaccination and most receptive subgroups, we can design more tailored interventions to increase uptake.

Supported: By National Institutes of Health; National Cancer Institute

Understanding and Responding to Concerns about Diabetes Risk and Symptomatology in Cancer Patients with Type 1 Diabetes

NICHOLAS DE LAHUNTA, NIKHIL D. THAPA, HENRY G. MILLS, SR., CAMILLA V. KILPATRICK, ANNE C. BEAL, MARYSE BEAUDIN, Paris, France, Lafayette, CA; Lyon, France, Swiftwater, PA; Bridgewater, NJ; Cambridge, MA

Background: The prevalence of diabetes among cancer patients has been increasing, and there is growing concern that diabetes may negatively impact survival and quality of life for cancer patients. We aimed to identify patient and provider factors that are associated with diabetes risk and symptomatology in cancer patients with type 1 diabetes.

Methods: We conducted a cross-sectional survey of patients with type 1 diabetes (N=122) in a large urban hospital system. We used a modified version of the Short Answer Diabetes Questionnaire to assess diabetes risk and symptomatology. Logistic regression models were used to identify predictors of diabetes risk and symptomatology.

Results: Patient factors associated with diabetes risk and symptomatology included age, gender, and diabetes duration. Provider factors associated with diabetes risk and symptomatology included provider education and experience in diabetes care. The most common concerns reported by patients were related to diabetes management and fear of hypoglycemia.

Conclusion: Diabetes risk and symptomatology in cancer patients with type 1 diabetes are multifactorial and influenced by both patient and provider factors. Further research is needed to identify effective strategies for managing diabetes in this population.

Supported: By National Institutes of Health; National Cancer Institute

Depressive Symptoms and Glycemic Control among Puerto Rican Adults with Diabetes

JOSIEMER MATTIE, LUIS M. FALCON, KATHERINEL. TUCKER, Boston, MA, Lowell, MA

A bidirectional relationship between depression and diabetes risk has been suggested. Less is known about the dynamics between depressive symptomatology and glycemic control among individuals already at risk of both conditions. We aimed to examine the prospective bidirectional associations between depressive symptomatology and glycemic control. We used data from 488 participants of the Boston Puerto Rican Health Study (mean [SD] age= 58.9 [17.2]) y with type 2 diabetes (fasting plasma glucose ≥ 126 mg/dl or use of medication). At baseline, participants were categorized as having uncontrolled hemoglobin A1c (≥7%) vs. controlled, and as having depressive symptomatology (Center for Epidemiological Studies-Depression (CES-D) score ≥16) vs. not. Categories for 2-year changes in glycemic control were set as (≥3-improved; ≥3 to <5-stable; <5-% worsened; 2-year changes in CES-D score as (≥3-improved; ≥3-stable; ≥3-worsened. In logistic regressions adjusted for sociodemographic and lifestyle variables and number of medical conditions, having baseline depressive symptomatology was associated with 1.96 (95% CI: (1.10, 3.56; p<0.022) higher odds of having worsened hemoglobin A1c at 2-year compared to keeping it stable. Baseline uncontrolled hemoglobin A1c was not associated with change in depression score. When modeling 2-year change categories as predictors, improved depression score (vs. stable) was associated with lower odds (0.42 (0.21, 0.81); p=0.3) of worsened hemoglobin A1c, while worsened glycemic control (vs. stable) was associated with lower odds (0.40 (0.21, 0.78); p=0.007) of improved depression score.

In conclusion, a bidirectional association between changes in depressive symptomatology and glycemic control over 2 years among individuals with type 2 diabetes.
diabetes suggests that timely attention to both conditions should be given simultaneously. Interconnected diabetes and depression management practices should be recommended for adults with diabetes.

Supported By: National Heart, Lung, and Blood Institute (K01HL129951, F99HL105189), National Institute on Aging (P01AG023394)

1597-P

Differences in Risk Factor Profile between Carotid Intimal Medial Thickness and Pulse Wave Velocity in African-Americans with Type 2 Diabetes

AFIBAMI AYOBAMI, AJIBOLA M. ADEDAOY, FASISA TDEL, ARYE KREMER, NICOLE MASTROIPSIGNANI, CARL ROSENBERG, PAUL DREZEN, JOHNLAROSA, LOUIS SALCICCIOLI, MOHAMED BOUTJDIR, CLINTON BROWN, MDR SALIFU, AHMED BAKILLAH, JASON LAZAR, Brooklyn, NY

Background: Diabetes is a robust risk factor for cardiovascular events which is marked in African-Americans for reasons that may be attributed to socioeconomic and biologic vulnerabilities. Both structural (arterial thickening) and functional (arterial stiffness) abnormalities of the vasculature are predictive of incident clinical events. Study was to determine the risk factors and relationship between large artery stiffness and carotid intimal thickness in African Americans with type 2 diabetes.

Methods: 125 patients with diabetes were recruited from medical clinics. Medical information was obtained via interview and electronic medical record review. Large artery stiffness was assessed by carotid-femoral pulse wave velocity (PWV) using applanation tonometry. Carotid Intimal Medial Thickness (CIMT) was obtained using B-mode ultrasound image analysis of the common carotid artery. Statistical analysis was done using SPSS version 23.

Results: Mean age 60±8 years, 64% female. 82% hypertension, dyslipidemia 83%, diabetes duration 10.2±7.6 years, Mean HbA1C=8.1±2.2%. Mean CIMT=0.68±0.15, PWV=8.62±2.9. There was no significant association between PWV and CIMT. CIMT positively correlated with gender (r=0.302, p<0.001), smoking (r=0.278, p=0.002), creatinine (r=0.260, p=0.008), triglycerides (r=0.279, p=0.002), pooled cohort score (r=0.353, p=0.001), and negatively with HDL (r=-0.196, p=0.031). PWV positively correlated with creatinine (r=0.360, p=0.001), duration of diabetes (r=0.195, p=0.037) and age (r=0.259, p=0.001) and pooled cohort score (r=0.248, p=0.003). After adjusting for cardiovascular risk factors, gender (β=2.000, p=0.019), and age (β=0.119, p=0.018) independently predict PWV but not CIMT.

Conclusion: Our findings indicate that PWV and CIMT differ in risk factor profile in African Americans with type 2 diabetes mellitus. Further studies are needed to clarify mediating factors.

Supported By: New York State Department of Health

1598-P

Copper Is Associated with Metabolic Syndrome and Fasting Blood Glucose in Non-Hispanic Black—Results from National Health and Nutrition Examination Survey

XIAOWEI HE, JR., YUN YU, SR., DINGLIN LOU, SR., WEI TANG, SR., Nanjing, China

Background: The metabolic syndrome is a cluster of risk factors which predicts future cardiovascular disease and type 2 diabetes. Evidence have showed that a disorder in serum Copper (Cu) level could have effects on human health. However, little data are available regarding how serum Cu affects metabolic syndrome in adults.

Method: Data from 3,375 subjects were examined from a nationally representative sample of the U.S. adults in the National Health and Nutrition Examination Survey 2011-2014. The metabolic syndrome was defined as satisfying three or more of the five criteria from the National Cholesterol Education Panel definition. Multivariate logistic and linear regression were used to investigate the associations of serum Cu levels with metabolic syndrome prevalence and its component.

Results: In the logistic models, non-Hispanic black with the highest serum Cu levels demonstrated a greater increase in risk of metabolic syndrome (OR: 2.69, 95% CI: 1.08-6.70, P for trend=0.001) when compared to those with the lowest serum Cu levels. Moreover, we identified a remarkable association between serum Cu levels and fasting blood glucose concentration in non-Hispanic black (OR: 2.44, 95% CI: 1.04-5.76, P for trend=0.031). No significant associations between serum Cu level and other components of metabolic syndrome were observed, regardless of race. In the linear regressions, a strong positive association between serum Cu levels and fasting blood glucose was also observed (coefficient=0.231, 95% CI: 0.053-0.409, P<0.001) in non-Hispanic black.

Conclusion: Our results provide the first epidemiological evidence that serum Cu concentrations may be positively associated with the prevalence of metabolic syndrome and with fasting blood glucose in non-Hispanic black. Further clinical and animal studies are urgently needed to clarify the putative causal relationships.

Supported By: National Natural Science Foundation of China
Background: Intake of sufficient dietary fiber has been recommended for glucose control, and typically low fiber intake is observed in the general population. The role of fiber in glycemic control in reported literature is inconsistent and few reports are available in populations with type 1 diabetes (T1D).

Methods: We conducted a cross-sectional analysis of data from the CACTI study (n=1257; T1D: n=568; nondiabetic controls: n=689) collected between March 2000 and April 2002. Participants completed a validated food frequency questionnaire, a physical examination and fasting biochemical analyses (12h fast) at screening visit. We used linear regression models to examine associations of total dietary fiber with HbA1c as a continuous variable. Models were stratified by diabetes status, and adjusted for age, sex, and total calories, and diabetes duration in the T1D group. We also examined correlations of fiber with HbA1c.

Results: Baseline dietary fiber intake and HbA1c in the T1D group were 16g (median [IQ]: 11-22g) and 7.9±1.3% mean (SD), respectively, and in the nondiabetic controls were 15g (median [IQ]: 11-21g) and 5.4±0.4%, respectively. Pearson partial correlation coefficients revealed a significant but weak inverse association of total dietary fiber with HbA1c when adjusted for age, sex, diabetes status and total calories (r= -0.07, p=0.01). In adjusted linear regression models, total dietary fiber was significantly and inversely associated with HbA1c in the T1D group (estimate (beta±SE)= -0.32±0.15, p=0.034), as well as in the nondiabetic controls (-0.10±0.04, p=0.009). Thus, at observed levels of intake, total dietary fiber reveals a protective association against poor glycemic control in T1D adults and in nondiabetic controls.

Conclusion: Our results support the conclusion that there is no causal association between vitamin D and diabetes and prediabetes using a bi-directional Mendelian Randomization approach in a Chinese population. MR studies using 1,25-dihydroxyvitamin D and large intervention trials are needed to further validate the findings.

Supported By: National Natural Science Foundation of China; Shanghai Jiao Tong University School of Medicine; Science and Technology Commission of Shanghai Municipality; Commission of Health and Family Planning of Putong District; the Shanghai Municipal Commission of Health and Family Planning
Epidemiology—Nutrition

1606-P
The Impact of Obesity and Lifestyle Status on Cardiovascular Risk Factors in Children and Adolescents with Type 1 Diabetes (T1D)
ANNA-MARIA LAMPOUSI, DIMITRIOS E. DELIS, SR., MARIA KATZIFPSALTI, ANDRANI VAEZELI, Athens, Greece.

Cardiovascular disease is more frequent in patients with T1D than the general population. The aim of the study was to examine the impact of obesity, diet and physical activity (PA) on common cardiovascular risk factors in youth with T1D. Cross-sectional analyses were performed using data from 96 T1D subjects (mean age 13.4 ± 2.7 years, females 57%), median disease duration 5.3 range 3.5-8.4 years). Dietary intake was evaluated by a single 24-hour dietary recall and a food frequency questionnaire (FFQ). Diet quality was assessed with the KDIDMED test. The ENERGY-child questionnaire was used for the assessment of PA. Systolic (SBP), diastolic (DBP) blood pressure, HbA1c levels and lipid profile were evaluated. The prevalence of overweight/obesity was 31%. Overweight/obese individuals were in higher SBP percentile, compared to those with normal weight (68.59 ± 26.58 vs. 51.77 ± 26.72, P = 0.006). In multiple regression analysis, higher BMI z-score, was associated with higher HbA1c (standardized β = 0.334, P = 0.002, R² = 0.268) and higher triglycerides (standardized β = 0.224, P = 0.05, R² = 0.095). Most participants (80%) abstained from optimal Mediterranean Diet (MD). Lower KDIDMED score was associated with higher HbA1c (standardized β = -0.432 P < 0.001, R² = 0.268). Partial correlation analyses after controlling for confounding factors revealed that BMI z-score was negatively correlated with low fat dairy products/df (r = -0.315, P < 0.05), HbA1c was positively correlated with high fat dairy products/df (r = 0.305, P < 0.05) and SBP percentile was negatively correlated with total milk and yogurt portions/df (r = -0.313, P < 0.05). Moreover, higher participation in sports (hours/week), was associated with lower DBP percentile (standardized β = -0.283, P = 0.015, R² = 0.080). The maintenance of a healthy body weight and a physically active lifestyle, was accompanied by lower BP levels in the participants of this study. Greater adherence to MD was associated with lower HbA1c.

1607-P
Correlation between Niacin and Iron Consumption and Diabetes Prevalence among Different Sex, Age, and Ethnic Groups in the U.S.
YIMING ZHOU, NANA CHEN, DA LI, WUPING SUN, SHI-HE SHENG ZHOU, Boston, MA, Nagoya, Japan, Shenyang, China, Shenzhen, China, Dalian, China.

Grain fortification with B vitamins (thiamin, riboflavin and niacin) and iron caused a significant increase in niacin and iron, which affect the body’s redox status and induce insulin resistance at high levels. The purpose of the present study was to investigate the correlation between the U.S. per capita niacin and iron consumption and the prevalence of type 2 diabetes by sex, age, and race. The data on the per capita nutrient consumption in 1960-2010 were from the Economic Research Service (ERS) of the U.S. Department of Agriculture. The ERS data showed that the per capita consumption of niacin and iron has increased from 16 mg/d and 12.5 mg/d to 34 mg/d and 24.5 mg/d, respectively from 1930s to 1990s, and thereafter remained fairly constant. This increase was mainly contributed by fortified grains or refined grains. The data of diabetes prevalence were from the Center for Disease Control (CDC). The data showed that the prevalence of diabetes began to increase from 1960s, with two rapidly increasing periods: from 1960s to early-1970s, and from 1990 to the early-2010, especially in some Southern States (e.g., Mississippi, South Carolina, and Louisiana, where grain fortification is mandatory), while the prevalence of diabetes remains relatively stable during the 1980s. We found that the prevalence of diabetes in the U.S. was strongly correlated with the per capita niacin and iron consumption (both r > 0.9). We further analyzed the correlations by age, sex, and race, and also found close correlations between the nutrient consumption and the prevalence of diabetes among sex groups, different racial groups, and different age groups. In conclusion, excess niacin and iron intake may play an important role in the increased prevalence of type 2 diabetes in the U.S.

1608-P
Dietary and Media Habits of Young Children in Mumbai
JASREENA NIJJAR, ANNA C. REVETTE, Boston, MA

LMIC are increasingly affected by the obesity pandemic and, it is estimated that by year 2030, there will be 80 million people with diabetes in India. Of concern is the emerging threat of obesity and type 2 DM among children. In 2019, World Health Assembly recognized food marketing as a key determinant of childhood dietary patterns, yet few studies in India have assessed exposure to media as a key NCD risk behaviors among children. This qualitative study explores children’s dietary and media use patterns, and aims to identify the ways in which young children in Mumbai are exposed to food marketing. Interviews and focus groups were conducted in June 2017 with purposively sampled dyads that included children aged 7-12 years and their mothers (n=34) from low to middle-income communities in Mumbai. Analysis of data found that children frequently consume packaged food, and characterized it as their favorite type of food. Television proved to be an influential source of information for most children, with most watching between two and four hours during the weekdays. Children reported learning about new food products primarily from TV advertisements. Most children could acquire their favorite food, either by purchasing it themselves or by convincing family members. Use of other forms of media, such as computers, were less prevalent, but most children did report using a mobile phone, which most often belonged to a family member. Parents identified children’s preference for unhealthy food, cost, limited time as barriers to a healthy diet and reported conflicts with their children about food requests. Additionally, most parents confirmed that TV played a significant and negative role in these arguments. Changing food environments and replacement of traditional diets have been found to have deleterious consequences for children. Investing in understanding dietary behaviors and communication activities of young children in Mumbai will support the development of appropriate context-specific intervention strategies at this crucial age.
Hemodialysis (HD)-Mediated Improvements in Insulin Resistance Are Correlated with Nutritional Status in Patients with Type 2 Diabetes

SATOSHI FUKUSHI, JUNICHIRO HASHISUCHI, MASATOSHI HAYASHIDA, RICA ETOMI, KENJI SAWASE, YUTAKA MORI, KAZUNORI UTSUMOIYAMA, TAKASHI HARADA, Kagasaki, Japan, Tokyo, Japan

Objective: Changes in C-peptide index (CPI) before and after hemodialysis (HD) were compared to explore factors associated with insulin resistance in diabetic patients receiving HD.

Methods: Fasting blood samples were drawn from type 2 diabetic patients receiving maintenance HD but not insulin therapy at our clinic before HD on the first day of the week they went on HD (pre-HD) as well as on the next day (post-HD) and CPI was calculated.

Results: The mean post-HD CPI was significantly lower than the mean pre-HD CPI (6.7 ± 2.7 ng/mL vs. 8.1 ± 3.3 ng/mL) in the 19 type 2 diabetic patients (men/women, 12/7) included in the study. The rate of decrease in CPI was strongly positively correlated with geriatric nutritional risk index (GNRI) (R² = 0.692) in these patients, while it was not correlated with their glycoalbumin (GA) or fasting glucose values.

Conclusions: Despite reports that HD leads to resolution of uremia and excessive fluid overload resulting in improvements in insulin resistance, to date, very few reports compared insulin resistance before and after HD. This study showed that the rate of decrease in CPI was not increased in patients with favorable glycemic control but significantly increased in those with favorable nutritional status, suggesting that the patient’s overall status may have a role to play in HD-mediated improvements in insulin resistance in the short term.

Figure.

Comorbidity of Diabetes and Chronic Sleep Disturbances and Consumption of a Mediterranean-Style Diet

HEIDI GUER, Ann Arbor, MI

Objective: This study assessed whether comorbidity of diabetes and chronic sleep disturbances was associated with less healthy dietary consumption, defined as a Mediterranean-style Diet, compared to adults with only one or neither of the conditions.

Research Design and Methods: Participants were selected from the Health and Retirement Study (HRS). Diabetes status and chronic sleep disturbances were assessed during the 2010 interview. Participants were categorized into one of four groups: no sleep disturbances or diabetes, sleep disturbances, diabetes, or sleep disturbances and diabetes. 7,423 participants completed a food frequency questionnaire by mail from which the alternative Mediterranean Diet (aMedDiet) score was assessed. Logistic regression was used to determine the odds of consuming an aMedDiet based on comorbidity of diabetes and chronic sleep disturbances. Models were stratified by gender.

Results: After adjusting for age and caloric intake, men with diabetes were more likely to consume an aMedDiet in the highest quartile (OR 1.45; 95% CI 1.11-1.91) than men with neither chronic sleep disturbances nor diabetes. The magnitude of the association increased after adjustment for additional demographic and health variables (OR 1.70, 95% CI 1.25-2.29). Women with sleep disturbances were less likely to consume an aMedDiet than those without sleep disturbances. The reduction in the odds of consuming an aMedDiet was greatest among women with comorbidity of the two conditions (OR 0.53, 95% CI 0.37-0.77) yet was also significant among those with chronic sleep disturbances alone (OR sleep disturbances 0.71, 95% CI 0.56-0.90). The results in women were attenuated after multivariate adjustment.

Conclusions: Chronic sleep disturbances reduce healthy dietary intake in adults with diabetes. 

Supported By: National Institute on Aging (U01AG009740)

Insulin Therapy and Breast Cancer Risk

CECILE PIOT, MIRUNA DRAGOMIR, PETER BOYLE, PHILIPPE AUTIER, Écuyé, France, Lyon, France

Some observational studies have suggested an association between insulin therapy and cancer risk. Using a meta-analytical approach, the risk of breast cancer in diabetic patients treated with insulin was compared to the risk in diabetic patients treated with a non-insulin therapy (NIT). A systematic literature search was conducted in the PubMed database from inception to October 2017. Studies with a prospective design including nested case-control and case-cohort studies were selected. Summary relative risks (SRR) of breast cancer associated with the use of any type of insulin therapy compared to NIT were computed using a random-effect model. Three subanalyses were carried out: one according to the adoption of a new-user design (i.e., including only new users of a drug) vs. a prevalent user design (i.e., including both new and past users of a drug); one according to the type of comparator (specific NIT vs. any type of NITs); and one according to the type of diabetes. A total of 12 studies, representing 1,392,040 diabetics and 15,430 breast cancer cases, were included in the analysis. Overall, the SRR of breast cancer associated with the use of any type of insulin therapy compared to NIT was 1.02 (95% CI: 0.95, 1.09) among women and 1.01 (95% CI: 0.97, 1.05) among men. The SRR was higher among newly diagnosed diabetic patients compared to previously diagnosed diabetic patients (1.05 vs. 0.98) and among diabetic patients taking insulin compared to diabetic patients taking a non-insulin therapy (1.05 vs. 1.00).

Conclusions: In adults with diabetes, insulin therapy is associated with a slightly increased risk of breast cancer compared to non-insulin therapy, with the risk being slightly higher among newly diagnosed diabetic patients and among diabetic patients taking insulin compared to diabetic patients taking a non-insulin therapy.
of breast cancer associated with insulin use was 0.97 (95% CI: 0.87, 1.08) with a high degree of heterogeneity between studies (I²=60%, p<0.01) and no evidence for publication bias. In all three sub-analyses, the SRR remained close to 1.0 and statistically non-significant. The heterogeneity was reduced in studies restricted to T2DM patients, in studies with a new-user design and in studies with a specific NIT used as comparator (I²=20%, 21% and 0%, respectively). Heterogeneity was increased in studies using a prevalent user design and in studies with a no/never use as comparator (I²=70% and 73%, respectively). This meta-analysis showed no evidence for an association between breast cancer occurrence and insulin therapy prescription history when the comparators are other NITs. The marked differences in heterogeneity indicate that studies with a new-user design or with a specific NIT as comparator are probably less affected by confounding and biases.

### 1614-P

**Thiazolidinediones and Reduced Risk of Incident Bacterial Abscesses in Adults with Type 2 Diabetes—A Population-Based Cohort Study**

CHIA-HSUIN CHANG, JIUN-LING WANG, YAA-HUI DONG, WEN-CHEN KO, LI-CHIU WU, LEE-MING CHUANG, PAU-CHUNG CHEN, Taipei, Taiwan; Taiwan, Taiwan, Taiwan

**Objective:** Previous research has suggested that peroxisome proliferator-activated receptor-γ agonists (PPAR-γ) may play an important role in immune-modulation. We examined whether PPAR-γ agonists (thiazolidinediones) were associated with the incidence of bacterial abscess among patients with type 2 diabetes.

**Research Design and Methods:** This retrospective cohort study included 46,986 propensity-matched patients diagnosed with type 2 diabetes between 2000 and 2010. We compared the incidence of bacterial abscesses and the incidences of two subclasses: liver and non-liver abscesses, between groups treated with either metformin plus a thiazolidinedione (M+T, N=7831) or metformin plus a sulfonylurea (M+S, N=39,155). Data were retrieved from a population-based Taiwanese database. We estimated hazard regression models.

**Results:** During a median follow-up of 4.5 years, the adjusted rate of incident bacterial abscess was lower with M+T than with M+S treatment (1.03 vs. 1.15 per 1000 person-years). M+T was associated with a reduced risk of bacterial abscess (adjusted HRs: 0.58, 95% CI: 0.42-0.80 for bacterial abscess; 0.54, 95% CI: 0.28-1.07 for liver abscess; and 0.59, 95% CI: 0.41-0.85 for non-liver abscess). The results did not change materially, after accounting for unmeasured confounding factors and differential censoring between the two treatment groups. Rosiglitazone and pioglitazone, in comparison, were associated with the incidence of bacterial abscess among patients with type 2 diabetes.

**Conclusions:** We found that M+T had a substantial protective effect in reducing the incidence of bacterial abscesses. These findings merit further investigation.

**Supported By:** Taiwan Ministry of Science and Technology

### 1615-P

**Twelve-Month Changes in HbA1c, Fasting Plasma Glucose, and Weight among Patients with Type 2 Diabetes in 37 Countries—DISCOVER**


**Background:** DISCOVER (NCT02227623) is a 3-year, observational study of patients with type 2 diabetes initiating second-line glucose-lowering therapy in 37 countries. We report change from baseline in HbA1c, fasting plasma glucose (FPG) and weight over 12 months.

**Methods:** HbA1c and weight were assessed in patients who had values recorded for these variables at baseline and 12 months (HbA1c, N = 7225; weight, N = 10,332). FPG was assessed in patients who had FPG values at baseline and 12 months, but who had HbA1c unreported at either time point (N = 1788). Patients were categorized by second-line therapy, and changes over 12 months were adjusted for baseline values using least-squares means.

**Results:** Overall mean (SD) changes over 12 months were: HbA1c, -1.1% (1.6%); FPG, -34.2 mg/dL (59.4 mg/dL); and weight, -0.5 kg (6.5 kg). At 12 months, the overall mean (SD) HbA1c value was 7.3% (1.2%), ranging from 7.0-7.3% in all treatment categories except insulin (8.0% Table). After initial baseline adjustment, changes in HbA1c were comparable across treatment categories. Weight increased in patients receiving a sulphonylurea or insulin, and decreased in patients receiving a dipeptidyl peptidase 4 inhibitor.

**Conclusions:** HbA1c and FPG were reduced substantially after 12 months in all treatment categories, with overall mean values only slightly above guideline-recommended targets.

**Supported By:** AstraZeneca

### 1616-P

**Using Claims and Consumer Wearable Devices Data to Quantify Influenza-Related Outcomes among Type 2 Diabetes Patients—A Large Population Study**


**Influenza causes substantial morbidity in people with diabetes; annual vaccination is recommended. We conducted a retrospective study of influenza-related outcomes (IRO) among fully insured type 2 diabetics from a large U.S. payer over a 1 year period covering the 2016-17 influenza season. We used bivariate analysis (54,656 diabetics, mean age 54.8 years, s.d. = 10.2) to compare IRO’s inferred from claims data against IRO’s for 113.016 age and gender matched nondiabetics. Diabetics had more influenza events (per ICD-9 and ICD-10 codes, 1.96% vs. 1.37%, p<0.001), and were prescribed more influenza antivirals per 100 ppl (27.1 vs. 22, p<0.001). Within 2-weeks and 4-weeks after a medical claim for influenza, diabetics with influenza had more observed hyperglycemic events than in a comparable non-influenza period in the same year (0.91% vs. 2.18%, p<0.001), with substantial increases in pneumonia, sepsis and coronary disease (5.5% vs. 0.7%, 5.5% vs. 3.5%, 1.8% vs. 0.3%, p<0.001), and more outpatient antibiotic use per 100 people (54.5 vs. 18.9, p<0.001). 8.2% of type 2 diabetics (vs. 9.1% controls, p<0.001) used commercially available activity and sleep trackers, sharing data through an insurer provided wellness platform. Activity trackers showed that diabetics slept fewer hours compared to controls (6.48 vs. 6.69 hours, p<0.001), and had statistically significant changes in sleep and walking habits in the days around an influenza event as compared to baseline (about 2% more of the night spent restless and 10% fewer steps). This is the first population scale study to use medical claims linked with activity tracking data to quantify the behavioral and clinical effects of influenza in type 2 diabetes. These data highlight the impact of influenza on glycemic control and the daily lives of the Diabetic population, and reinforce the need for annual influenza vaccine, as recommended by the WHO and other global public health bodies.

**Supported By:** Sanofi

### 1617-P

**Association of Visceral Fat and Liver Fat, Not Thigh Muscle Area, with Attenuation, with the Incidence of Type 2 Diabetes**

KYOKO SATO, SHINCHIRO UEHARA, MIKIKO SHIBATA, YONEZO HIKITA, WILFRED Y. FUJIMOTO, EDWARD J. BOYKO, TOMOSIGE HAYASHI, Osaka, Japan, Seattle, WA

**Visceral fat, liver, and skeletal muscle are all major target organs of insulin and play key roles in the pathophysiology of type 2 diabetes. Not well known is whether visceral fat, liver fat, and thigh skeletal muscle area or fat directly measured by computed tomography (CT) are independently associated with the incidence of type 2 diabetes. A prospective cohort study, 1228 nondiabetic Japanese men and women were included. Intra-abdominal visceral fat, liver fat, and thigh skeletal muscle area were measured by computed tomography, and the incidence of type 2 diabetes was assessed during a median follow-up of 11 years (1995-2005). The main outcome was the incidence of type 2 diabetes. The main independent variables were visceral fat, liver fat, thigh skeletal muscle area, and BMI. The adjusted hazard ratio of visceral fat, liver fat, and thigh skeletal muscle area for the incidence of type 2 diabetes was 1.04, 1.05, and 1.01, respectively. These results suggest that intra-abdominal visceral fat and liver fat, but not thigh skeletal muscle area or fat, are independently associated with the incidence of type 2 diabetes.**

**Supported By:** AstraZeneca
fat area (IAFA), liver-to-spleen (L/S) attenuation ratio to assess liver fat, and mid-thigh muscle area and attenuation were measured by CT. Low CT attenuation of liver and muscle reflects greater liver and intramuscular lipid content. Insulin resistance was assessed by HOMA-IR. Type 2 diabetes was diagnosed as fasting plasma glucose level ≥126 mg/dL, HbA1c ≥5.5%, or taking oral hypoglycemic medications or insulin. Discrete-time logistic hazard model was used. During the 7886 person-years of follow-up (median follow-up period, 7 years), 95 subjects developed type 2 diabetes. IAFA and L/S ratio, not thigh muscle area, were independently associated with the risk of type 2 diabetes. When thigh muscle attenuation was substituted for its area, results were similar. Those of tertile 2 and 3 of thigh muscle area and attenuation were 2.01 (1.01-3.97) and 2.05 (1.04-4.08), respectively, compared to tertile 3. However, those of tertile 2 and 3 of L/S ratio were 2.23 (95% CI, 0.94-5.31) and 3.16 (1.33-7.52), respectively, compared to tertile 1, and those for tertile 1 and 2 of L/S ratio were 2.01 (1.01-3.97) and 2.05 (1.04-4.08), respectively, compared to tertile 3. However, those of tertile 2 and 3 of thigh muscle area were 0.76 (0.32-1.78) and 0.64 (0.24-1.69), respectively, compared to tertile 1. When thigh muscle attenuation was substituted for its area, results were similar to the above model.

In conclusion, both greater amounts of visceral and liver fat, not thigh muscle area nor attenuation, were independently associated with the risk of type 2 diabetes.

1618-P Chronic Kidney Disease (CKD) in U.S. Adults with Self-Reported Cardiovascular Disease (CVD)—A National Estimate of Prevalence by KDIGO 2012 Classification
TONGTONG WANG, YUZHIXI, ROBERT N. LUBWAMA, CAROL KORO, KINNINWORTH, NJ, Chapel Hill, NC, North Wales, PA
Overall prevalence of CKD in the U.S. adult general population was estimated to be 14.8%. But data on the prevalence of CKD among CVD populations are limited.

Using the NHANES 2007-2014 data, we conducted a cross-sectional analysis of an adult sample with self-reported CVD (n=2325), aged ≥18 years, to assess prevalence of CKD in U.S. adults with CVD using KDIGO 2012 classification. Participants with CVD were identified based on self-reported personal interview data on a broad range of health conditions—congestive heart failure, coronary heart disease, angina, stroke, or heart attack. Appropriate sample weights were used to provide a national estimate.

Results of prevalence of CKD in U.S. adults with self-reported CVD are presented in Table 1. The prevalence of moderately to severely decreased renal impairment based on eGFR below 60 ml/min/1.73m² was 24.9%: 14.1% with Stage 3a, 7.8% with Stage 3b, and 3.0% with Stage 4 or 5. The prevalence of mildly decreased renal impairment (stage 2, eGFR 60-90 ml/min/1.73m²) was 45.2%, 36.6% with UAER=30-300 mg/g (normal to mildly increased albuminuria), 7.4% with UAER=30-300 mg/g (moderately increased albuminuria) and 1.1% with UAER>3000 mg/g (severely increased albuminuria).

This study confirms the high prevalence of CKD in CVD, and provides insights into distribution by CVD categories based on the KDIGO 2012 classification.
**1621-P**

**Efficacy of A1C in the Presence of HbC Trait Needs Evaluation**

**SARA M. BRIKER, JEAN DAMASCENE KABAKAMBIRA, RAFAL L. BAKER, JR., CHRISTOPHER DUBOSE, LILIAN MABUNDO, STEPHANIE T. CHUNG, DAVID B. SACKS, ANNE E. SUMMER, Bethesda, MD**

Hemoglobin C (HbC) trait is a Hb variant found in 15% of West Africans. Similar to HbS, HbC occurs because of a single nucleotide substitution on the beta-globin chain of hemoglobin. Many studies have evaluated whether HbS trait influences the diagnostic efficacy of A1C. Data on the effect of HbC trait on A1C is scant. Our goal was to determine by Hb-type the sensitivity and specificity of A1C as a diagnostic test for the detection of abnormal glucose tolerance (abnl-GT) in 369 blacks born in Africa and currently living in the Washington, DC area (age 38±10y (mean±SD), BMI 27.5±4.5 kg/m2). OGTT and Hb electrophoreses were performed. Abnl-GT was defined as fasting glucose ≥100 mg/dL or 2h glucose ≥140 mg/dL. A1C ≥5.7% was considered diagnostic for abnl-GT. The frequencies of normal Hb-type, HbS trait and HbC trait were: 82%, 14% and 4%, respectively. The prevalence of abnl-GT in each group was: 38%, 42%, and 50% (P=0.59), respectively. Sensitivity and specificity of A1C by group are provided in the Table. No one in the HbC trait group with abnl-GT was detected by A1C, hence, sensitivity was 0%. Furthermore, specificity of A1C in the HbC trait group was 100% as no one with normal glucose tolerance had A1C≥5.7%. The number of individuals with HbC trait was small but our findings suggest the need for greater investigation into the diagnostic efficacy of A1C in the presence of HbC trait.

**Table.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Hb-type</th>
<th>HbS Trait</th>
<th>HbC Trait</th>
</tr>
</thead>
<tbody>
<tr>
<td>sensitivity</td>
<td>47%</td>
<td>68%</td>
<td>0%</td>
</tr>
<tr>
<td>specificity</td>
<td>78%</td>
<td>77%</td>
<td>100%</td>
</tr>
</tbody>
</table>

**1622-P**

**Metformin and Risk of Hepatocellular Carcinoma in Taiwanese Patients with Type 2 Diabetes**

**CHIN-HSIANG TSAI, Taipei, Taiwan**

**Background:** Whether metformin may reduce hepatocellular carcinoma (HCC) risk requires confirmation.

**Methods:** Newly diagnosed type 2 diabetes patients during 1999-2005 with 2 or more prescriptions of antidiabetic drugs were enrolled from the Taiwan’s National Health Insurance. A total of 173917 ever users and 21900 never users of metformin were identified (unmatched cohort). A 1:1 matched-pairs cohort of 21900 ever users and 21900 never users based on propensity score was created. Hazard ratios were estimated by Cox regression incorporated with the inverse probability of treatment weighting using PS. Additionally, the interactions with aspirin and statin were evaluated.

**Results:** In the unmatched cohort, 619 never users and 2642 ever users developed HCC, with respective incidence of 668.0 and 330.7 per 100,000 person-years and overall hazard ratio of 0.49 (95% confidence interval: 0.45-0.54). The hazard ratio for the first (<25.7 months), second (25.7–56.9 months) and third (>58.9 months) tertile of cumulative duration of metformin therapy was 0.89 (0.81-0.98), 0.50 (0.46-0.56) and 0.23 (0.21-0.26), respectively. Analyses in the matched cohort showed an overall hazard ratio of 0.69 (0.62-0.78) and the hazard ratio for the respective tertile was 1.28 (1.10-1.50), 0.68 (0.57-0.82) and 0.35 (0.29-0.44). A significant interaction with metformin was observed for aspirin and statin.

**Conclusions:** Metformin is associated with a reduced risk of HCC in a dose-response pattern. Users of both metformin and aspirin or statin have the lowest risk.

**1623-P**

**Health Disparity in Diabetes Care—Impact of Community Health Representative-Led Patient Activation and Engagement**

**VALLABH SHAH, VERNON S. PANKRATZ, DONICA M. GHADATE, CHRISTOPHER DUBOSE, LILIAN MABUNDO, STEPHANIE T. CHUNG, DAVID B. SACKS, ANNE E. SUMMER, Bethesda, MD**

Hemoglobin C (HbC) trait is a Hb variant found in 15% of West Africans. Similar to HbS, HbC occurs because of a single nucleotide substitution on the beta-globin chain of hemoglobin. Many studies have evaluated whether HbS trait influences the diagnostic efficacy of A1C. Data on the effect of HbC trait on A1C is scant. Our goal was to determine by Hb-type the sensitivity and specificity of A1C as a diagnostic test for the detection of abnormal glucose tolerance (abnl-GT) in 369 blacks born in Africa and currently living in the Washington, DC area (age 38±10y (mean±SD), BMI 27.5±4.5 kg/m2). OGTT and Hb electrophoreses were performed. Abnl-GT was defined as fasting glucose ≥100 mg/dL or 2h glucose ≥140 mg/dL. A1C ≥5.7% was considered diagnostic for abnl-GT. The frequencies of normal Hb-type, HbS trait and HbC trait were: 82%, 14% and 4%, respectively. The prevalence of abnl-GT in each group was: 38%, 42%, and 50% (P=0.59), respectively. Sensitivity and specificity of A1C by group are provided in the Table. No one in the HbC trait group with abnl-GT was detected by A1C, hence, sensitivity was 0%. Furthermore, specificity of A1C in the HbC trait group was 100% as no one with normal glucose tolerance had A1C≥5.7%. The number of individuals with HbC trait was small but our findings suggest the need for greater investigation into the diagnostic efficacy of A1C in the presence of HbC trait.

**Table.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Hb-type</th>
<th>HbS Trait</th>
<th>HbC Trait</th>
</tr>
</thead>
<tbody>
<tr>
<td>sensitivity</td>
<td>47%</td>
<td>68%</td>
<td>0%</td>
</tr>
<tr>
<td>specificity</td>
<td>78%</td>
<td>77%</td>
<td>100%</td>
</tr>
</tbody>
</table>

**1624-P**

**The Association between Lipid Profile Abnormalities and the Risk of Proteinuria in Japanese Men with Impaired Fasting Glucose or Type 2 Diabetes**

**SHINICHIRO UEHARA, KYOKO SATO, MIKIKO SHIBATA, KEIKO UE, HIROSHI KAMBE, MICHI MORIMOTO, TOMOSHIGE HAYASHI, Osaka, Japan**

Lipid profile abnormalities have been reported to be associated with cardiometabolic diseases, but it is not fully known whether lipid profile abnormalities are prospectively associated with the risk of proteinuria in subjects with impaired fasting glucose (IFG) or type 2 diabetes. Study subjects included 3801 Japanese men aged 40-55 years who had fasting plasma glucose ≥100 mg/dL, no proteinuria, eGFR >60 mL/min/1.73 m², and no history of cancer and were not taking antihypertensive, lipid-lowering, and hypoglycemic medications at baseline. The incidence of proteinuria was defined as “consecutive proteinuria” if it was detected twice consecutively as 1+ or higher on urine dipstick during the follow-up periods to exclude chance proteinuria as much as possible. Triglycerides, HDL-cholesterol, non-HDL-cholesterol, and LDL-cholesterol levels were obtained at baseline. During the 11-year follow-up period, we confirmed 221 cases of proteinuria. In Cox proportional-hazards analysis, higher level of triglycerides increased the risk of proteinuria and higher level of HDL-cholesterol decreased the risk of proteinuria. After adjustment for age, eGFR, fasting plasma glucose, hyper-tension status, alcohol consumption, regular physical activity, and smoking status, hazard ratios (HRs) for triglycerides levels of 100-149, 150-199, and ≥200 mg/dL were 1.07 (95% CI, 0.73-1.55), 1.22 (0.80-1.84), and 1.47 (1.01-2.13), respectively, compared with <100 mg/dL. The HRs for HDL-cholesterol levels of 40-59, 60-79, and ≥80 mg/dL were 0.52 (0.36-0.75), 0.52 (0.34-0.82), and 0.44 (0.22-0.92), respectively, compared with <60 mg/dL. However, neither HDL-cholesterol nor LDL-cholesterol were associated with the risk of proteinuria. In conclusion, higher level of triglycerides increased the risk of incident consecutive proteinuria and higher level of HDL-cholesterol decreased it in the middle-aged Japanese men with IFG or type 2 diabetes.

**Supported By:** Japan Society for the Promotion of Science

**1625-P**

**The Prevalence and Impact of Diabetes Mellitus among Undocumented Immigrants in an Indigent Care Program in Riverside, California**

**HAYLEY LEE, BISHOD L. ZAKHARY, MATTHEW A. FIREK, HEIDI LANGE, CLAUDIN A. GOMEZ, ANTHONY FIREK, Moreno Valley, CA**

**Background:** Acculturated undocumented immigrants (UI) in the U.S. with sedentary lifestyle and poor eating habits are at risk for diabetes mellitus (DM). UI also face adverse social, economic, and psychological stressors that may lead to poor clinical outcomes. No study to date has assessed DM prevalence and clinical outcomes among UI.

**Methods:** Riverside University Health System, a county health system, provides medical care for indigent patients including UI. 9,488 UI receiving indigent care as of March, 2017, 500 UI were randomly selected to assess DM prevalence and clinical outcomes.

**Results:** The mean age was 46.2 with more females (59%) accessing medical care. Over 95% were Hispanics and 74% were born in Mexico. Most
were married and only 11% worked full time. A majority of UI never smoked (67%), and only 18% consumed alcohol. The prevalence of DM was 27%, and diabetes were older than nondiabetics (52.2 vs. 43.8, p<0.001) with comparable BMIs (29.9 vs. 29.8, p=0.12). The mean hemoglobin A1c was 8.3 and insulin and oral anti-hyperglycemic medication use was 8% and 19%, respectively. The total clinic visits among diabetics was 19 compared to 13 in nondiabetics (p<0.018) while total emergency department visits were comparable between two groups (2 vs. 2, p=1.00). The use of prescription medications was higher in diabetics than nondiabetics (7 vs. 4, p<0.001). Diabetics had a higher rate of hypertension compared to nondiabetics (75% vs. 20%, p<0.001), but other clinical conditions were similar (congestive heart failure 1% vs. 3%, cancer 4% vs. 3%, depression 6% vs. 3%, chronic kidney disease 7% vs. 3%).

Conclusions: The prevalence of DM among UI is high with poor glycemic control. Diabetics had more clinic visits than nondiabetics and were taking more prescription medications. Despite high prevalence of DM, diabetes-related complication and comorbidity rates were low, which may be due to medical care access through the indigent care program.

1626-P Risk Factors for Sleep Apnea Syndrome in Diabetic Patients with a Focus on Comorbidities
SATSUKI KAWASAKI, HARUO MISAWA, RYO KANEDA, TETSUJI KONDO, YOSHINOBU KONDO, YASUO TERAUCHI, Furusawa, Japan, Yokohama, Japan
Diabetic patients often have various diseases such as vascular diseases and other comorbidities. Sleep apnea syndrome (SAS) is a serious disorder that may lead to acute deterioration due to nocturnal hypoxia. Among the 1,367 ambulant patients with type 2 diabetes (T2DM) who were being treated at our institution, 483 (313 men and 170 women) who agreed to undergo a portable sleep polygraph test were evaluated to identify risk factors for SAS, with a focus on microangiopathy and stable comorbidities. The rates of intracranial lesions, respiratory diseases, cardiovascular diseases, cancer, thyroid diseases, and mental illness were 22%, 9.9%, 39.8%, 16.1%, 7.7%, and 5.8%, respectively. The rates of microangiopathy were as follows: retinopathy (30.6%) and nephropathy (48.5%). The patients who had an apnea-hypopnea index (AHI) of 15±4.14±3.9 (mean±standard deviation) (15.8±14.5 in men and 12.8±13.8 in women). The prevalence of SAS (AHI>15) was 40.6% (127/313) in men and 29.4% (50/170) in women. Intracranial lesions, cardiovascular diseases, and cancer were more common among patients with SAS than among those without SAS (AHI>15)(p<0.05 each), while no such association was found for microangiopathy. Multivariate analysis adjusting for known risk factors for SAS (BMI, male gender, and age) identified BMI (odds ratio, 1.25; 95% confidence interval, 1.18-1.33; p<0.0001), male gender (2.11; 1.36-3.34; p<0.001), and intracranial lesions (1.74; 1.07-2.63; p<0.05) as independent risk factors for SAS. The intracranial lesions identified were stable and diverse, ranging from infarction and hemorrhage to benign brain tumor and encephalitis. The association of intracranial lesions with hypoxia may be related to the respiratory centers, although the underlying mechanism is unknown. Given the high prevalence of SAS, T2DM patients with obesity, male gender, and stable intracranial lesions should be carefully monitored for nocturnal hypoxia, particularly during emergency hospitalization.

1627-P Effect of Vitamin D Supplementation on Glucose Metabolism Biomarkers—A Meta-analysis of Randomized Controlled Trials
CECILE PIROT, PATRICK MULLIE, ALUNA MACACO, MIURINA DRAGOMIR, PETER BOYLE, PHILIPPE AUTIER, Ecouy, France, Lyon, France
Observational studies have linked higher serum concentrations of 25(OH)D with a reduced risk of diabetes. In order to assess the effect of vitaminD supplementation (VDS) on glucose metabolism biomarkers, a systematic review with meta-analysis of randomized-controlled trials (RCTs) was undertaken. RCTs published until February 2017 were selected in adults were: -0.06% (-0.12, 0.00) for HbA1c, -0.12 mmol/L (-0.20, -0.05) on HbA1c, FG, FI and HOMA-IR, respectively, with a majority of studies con- conducted in Europe and the Middle East. The summary MDs (95% confidence interval) were: -0.25% (-0.42, -0.08) for FG, -17.4 (-26.36, -9.11) for FI and -0.71 (-1.08, -0.32) for HOMA-IR, with high heterogeneity (I²=76%, 79%, 79% respectively). In Europe, the results were 0.01 (-0.06, 0.07) for FG, -0.59 (6.86, 5.68) for FI and -0.04 (-0.19, 0.10) for HOMA-IR, with lower heterogeneity (I²=21%, 48%, 0% respectively). In studies with high dose of vitamin D (≥ 100 µg/d) and sub- jects with baseline 25OHD ≤ 20 ng/mL, the summary MDs for HbA1c and FG were -0.09% (0.24, 0.07) and -0.05 mmol/L (-1.06, 0.06). The influence of VDS on glucose metabolism biomarkers seems to be marginal. The reasons underlying the heterogeneity of results across countries is unknown but dif- ferences in the conduct of RCTs cannot be excluded.

1628-P Distance from Glycemic Target at the Time of Add-On Initiation in Patients with Type 2 Diabetes (T2D) Failing Metformin Monotherapy in the United States
GAIL FERNANDEZ, HAKU HANNACHIN, JINIAN LIU, TONGTONG WANG, ANN MARIE MCNEILL, ALEX Z. FU, SWAPNIL RAJPATHAK, North Wales, PA, Kenilworth, NJ, Chapel Hill, NC, Washington, DC
While it is known that a substantial proportion of U.S. patients with T2D are not at glycemic target, the distance to glycemic target has not been adequately characterized, especially at the time of add-on initiation. The objective of the study was to quantify the distance from an HbA1c target of 7% among patients failing metformin monotherapy at the time of treatment intensification with an add-on agent. This retrospective study using Quintiles Electronic Medical Record database included patients with diagnosed T2DM on metformin monotherapy in such patients to be followed for 3 years, those with chronic diabetes complications or history of hypoglycemia; a total of 22,239 T2DM patients met the study criteria; mean age of 58.3 years, 51.2% were female, 10.8% of patients had a history of microvascular complications; 51% had a history of macrovascular complications. Median distance from HbA1c target was calculated as the median dif- fference of HbA1c from target of 7% at the time of add-on initiation was reported. A total of 22,239 T2DM patients met the study criteria; mean age of 58.3 years, 51.2% were female, 10.8% of patients had a history of microvascular complications; 51% had a history of macrovascular complications. Median distance from HbA1c target was calculated as the median dif- ference of HbA1c from target of 7% at the time of add-on initiation was 27.0% were ≥1% away from the target at the time of intensification. In this study, we found more than half of the metformin monotherapy patients were at least 1% away from glycemic target of 7% at the time of add-on initiation.

1629-P Individualized HbA1c Targets in People with Type 2 Diabetes Initiating Second-Line Therapy—The Global DISCOVER Study
KAMLESH KHUNTI, HUNGTA CHEN, JAVIER COS-ROZAPA, PETER FENICI, MARIJA B. GÖMANS, NIKLAS HAMMAR, KEVIN KENNEDY, MIKHAIL KOSIBOROD, STUART POCOCK, MARINA V. SHESTAKOVA, CHARLES SHOCKWILEY, FILIP STRAND, ANDREW MONT, LINONG JI, Leicester, United Kingdom, Gathersburg, MD, Barcelona, Spain, Cambridge, United Kingdom, Rio de Janeiro, Brazil, Molndal, Sweden, Kansas City, MO, London, United Kingdom, Moscow, Russian Federation, Osaka, Japan, Luton, United Kingdom, Beijing, China
Background: International guidelines recommend setting individual- ized HbA1c targets for people with type 2 diabetes (T2D). DISCOVER (NCT02322782) is an observational study of patients with T2D initiating second-line glucose-lowering therapy in 37 countries. We report the proportion of patients set individualized targets, the proportion meeting these targets after 1 year, and factors associated with meeting these targets.
Methods: Patients included had HbA1c data at baseline and at 1 year. Factors associated with meeting targets were assessed using multivariable logistic regression.
Results: Of the 1225 patients with complete HbA1c data who remained in the study after 1 year, 5,070 (70.2%) had been set an individualized glycemic control target. Targets were 7.0% for 2,513 patients (49.6%), < 7.0% for 2,073 patients, (40.9%) and > 7.0% for 484 patients (9.6%). Overall, 1,744 of these patients (34.3%) met their target after 12 months of follow-up (range across regions: -0.96% (-1.12, 0.00) for HbA1c, -0.12 mmol/L (-0.20, 0.00) for FG, -0.53 mmol/L (-1.17, -3.90) for FG, and -0.35 (-0.54, -0.15) for HOMA-IR. High heterogeneity between studies was observed for all biomarkers (I² > 70%) and no evidence for publication bias was noted. Important differences appeared between countries. In the Middle-East, the results were

ADA-Supported Research  Moderated Poster Discussion
Prediction of Adverse Pregnancy Outcomes among Women with Type 1 Diabetes

TINA COSTACOU, DEBRA RUBINSTEIN, TREVOR J. ORCHARD, Pittsburgh, PA

Women with type 1 diabetes are at a greater risk for adverse pregnancy outcomes (APO) compared with the general population, though factors relating to the occurrence of APO have not been well studied. We thus assessed predictors of APO among women with type 1 diabetes. Female participants (n=325; mean baseline age 28, duration 19 years) of a prospective cohort of childhood onset type 1 diabetes were selected for study. Among 320 with pregnancy data available, all pregnancies occurred after study entry (1986-1993). Of 1,522,526 eligible patients, 54% were female, median age was 65 years, and median HbA1c was 6.7%. The cohort representation by race, and prevalence of comorbidities by CVD status, are shown in the Table. Overall, 25% of patients had CVD, but this varied by race from 18.6% to 30.5%. The most prevalent comorbidities for all races included hypertension, hyperlipidemia, overweight/obesity, chronic kidney disease, neuropathy and heart failure, with rates generally higher among patients with CVD. Fetal infections were also common for those with CVD across subgroups, but especially for Asian patients with CVD (36.9%). In conclusion, patients with T2D and CVD had higher rates of common comorbidities vs. those without CVD, but rates varied by racial subgroups.

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Overall (%)</th>
<th>Asian (%)</th>
<th>Non-Asian (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>20%</td>
<td>16%</td>
<td>21%</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>25%</td>
<td>22%</td>
<td>26%</td>
</tr>
<tr>
<td>Overweight/obesity</td>
<td>45%</td>
<td>42%</td>
<td>47%</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>5%</td>
<td>4%</td>
<td>6%</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Heart failure</td>
<td>4%</td>
<td>3%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Supported By: AstraZeneca

1630-P

Relationship between Glycemic Control and Treatment Intensity in Patients with Type 2 Diabetes

KRISTY IGLAY, HAKIMA HANNACHI, SAMUEL S. ENGEL, XUEYING LI, DAVID J. O’CONNELL, LORI M. MOORE, SWAPNIL RAJPATHAK, Kenilworth, NJ

Previous studies have shown suboptimal glycemic control among patients with type 2 diabetes (T2D); however, the level of glycemic control has not been specifically evaluated for different degrees of treatment intensity. To assess this, we used the Quintiles Electronic Medical Record database to examine T2D patients >18 years with >1 encounter from Oct 2014 to Sept 2015, ≥1 year of available medical history, ≥1 HbA1c measure, and no insulin use at their last recorded encounter. Of the 678,447 eligible patients, median age was 65 years, 54% were female, and median HbA1c was 6.5%. The Table shows the distribution of HbA1c range vs. treatment intensity. Overall, 32% of patients had suboptimal HbA1c levels (<7%). Of those patients, 10% were untreated, 35% were on monotherapy, and 55% were not at goal despite being on 2 or 3+ agents. In patients with HbA1c ≥9%, 9% were untreated and 28% were on monotherapy. Among patients at the treatment target of <7%, only 24% were on dual or triple therapy, suggesting that patients on monotherapy who are not at goal were not consistently advanced to dual/ triple therapy. Results were generally similar when subgroups with/without cardiovascular disease were examined.

In conclusion, 32% of our cohort had suboptimal HbA1c control. Given the distribution of therapy, opportunity exists to initiate/intensify treatment to improve glycemic control in this population.

Table.

<table>
<thead>
<tr>
<th>Treatment Intensity</th>
<th>&lt;7%</th>
<th>≥7%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td>12%</td>
<td>88%</td>
</tr>
<tr>
<td>Biologic triple</td>
<td>25%</td>
<td>75%</td>
</tr>
<tr>
<td>Basal Insulin</td>
<td>35%</td>
<td>65%</td>
</tr>
</tbody>
</table>

Supported By: National Institutes of Health (DK34818); Rossi Memorial Fund

1631-P

Racial Patterns of Comorbidities in Patients with Cardiovascular Disease and Type 2 Diabetes

KRISTY IGLAY, HAKIMA HANNACHI, SAMUEL S. ENGEL, XUEYING LI, DAVID J. O’CONNELL, LORI M. MOORE, SWAPNIL RAJPATHAK, Kenilworth, NJ

Significant differences have been demonstrated in the risk of incident type 2 diabetes (T2D) and T2D-related complications by patient race. Because the presence of comorbidities can directly impact a physician’s selection of antidiabetic therapy, the current study sought to quantify differences in prevalence of diabetes-related comorbidities by race and cardiovascular disease (CVD) status in a large U.S. cohort. We conducted a retrospective study of T2D patients ≥18 years who had ≥1 encounter in the Quintiles Electronic Medical Record database from October 2014 to September 2015, as well as ≥1 year of medical history available. Of the 1,522,526 eligible patients, 54% were female, median age was 65 years, and median HbA1c was 6.7%. The cohort representation by race, and prevalence of comorbidities by CVD status, are shown in the Table. Overall, 25% of patients had CVD, but this varied by race from 18.6% to 30.5%. The most prevalent comorbidities for all races included hypertension, hyperlipidemia, overweight/obesity, chronic kidney disease, neuropathy and heart failure, with rates generally higher among patients with CVD. Fetal infections were also common for those with CVD across subgroups, but especially for Asian patients with CVD (36.9%). In conclusion, patients with T2D and CVD had higher rates of common comorbidities vs. those without CVD, but rates varied by racial subgroups.

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Overall (%)</th>
<th>Asian (%)</th>
<th>Non-Asian (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>20%</td>
<td>16%</td>
<td>21%</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>25%</td>
<td>22%</td>
<td>26%</td>
</tr>
<tr>
<td>Overweight/obesity</td>
<td>45%</td>
<td>42%</td>
<td>47%</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>5%</td>
<td>4%</td>
<td>6%</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Heart failure</td>
<td>4%</td>
<td>3%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Supported By: AstraZeneca

1632-P

Significant differences have been demonstrated in the risk of incident type 2 diabetes (T2D) and T2D-related complications by patient race. Because the presence of comorbidities can directly impact a physician’s selection of antidiabetic therapy, the current study sought to quantify differences in prevalence of diabetes-related comorbidities by race and cardiovascular disease (CVD) status in a large U.S. cohort. We conducted a retrospective study of T2D patients ≥18 years who had ≥1 encounter in the Quintiles Electronic Medical Record database from October 2014 to September 2015, as well as ≥1 year of medical history available. Of the 1,522,526 eligible patients, 54% were female, median age was 65 years, and median HbA1c was 6.7%. The cohort representation by race, and prevalence of comorbidities by CVD status, are shown in the Table. Overall, 25% of patients had CVD, but this varied by race from 18.6% to 30.5%. The most prevalent comorbidities for all races included hypertension, hyperlipidemia, overweight/obesity, chronic kidney disease, neuropathy and heart failure, with rates generally higher among patients with CVD. Fetal infections were also common for those with CVD across subgroups, but especially for Asian patients with CVD (36.9%). In conclusion, patients with T2D and CVD had higher rates of common comorbidities vs. those without CVD, but rates varied by racial subgroups.

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Overall (%)</th>
<th>Asian (%)</th>
<th>Non-Asian (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>20%</td>
<td>16%</td>
<td>21%</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>25%</td>
<td>22%</td>
<td>26%</td>
</tr>
<tr>
<td>Overweight/obesity</td>
<td>45%</td>
<td>42%</td>
<td>47%</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>5%</td>
<td>4%</td>
<td>6%</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Heart failure</td>
<td>4%</td>
<td>3%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Supported By: AstraZeneca

1631-P
Regardless of Subsequent Glycemic Progression, regular exercise and weight control, are recommended.

Impacts of the Kumamoto Earthquake 2016 on Glycemic Control in Diabetic Patients

TATSUYA KONDÔ, NOBUKAZU MIYAKAWA, HIROYUKI MOTOSHIMA, NORIO ISHI, MIYUTIYUKI IGATA, KAYO YOSHINAGA, DAISUKE KUKIDÔME, TAKAFUMI SENÔKUCHI, JUNJI KAWASHIMA, TAKESHI MATSUMURA, EICHI ARAKI, KUMAMOTO, JAPAN

In April 14th and 18th, 2016, Kumamoto area was severely damaged by massive M7 class earthquakes. To examine the effects of these earthquakes on glycemic control and stress factors in diabetic outpatients regularly cared in diabetic clinic of Kumamoto University Hospital, sequential HbA1c, glycated albumin, other biochemical parameters, life style associated questionnaire and Impact of Event Scale-Revised (IES-R) scores were analyzed. A total of 557 patients were enrolled and data were collected from 13 months before to 13 months after the earthquakes. In patients with type 1 diabetes (T1D) or specific types of diabetes due to other causes, glycemic control was not altered during the observational period. This glycemic stability in T1D may result from self-management of insulin doses (increase in % and decrease in 20% of patients). In patients with type 2 diabetes (T2D), HbA1c was decreased by 0.11% (from 7.33% to 7.72%) at 1-2 months after the earthquakes compared to that before the earthquakes, and increased at 3-4, 6-7 and 12-13 months after the earthquakes. The reduction of HbA1c at after 1-2 months in T2D was associated with “quick restoration of life-lines” and “sufficiency of sleep”. The glycemic deterioration after 3-4 months was related to “shortage of antidiabetic agents” and “insufficient amount of food,” and at after 12-13 months that was connected to “large-scale partial destruction of houses” and “changes in working environments.” IES-R, representing disaster associated stress levels were positively correlated with “age,” “delayed restoration of life-lines,” “self-managements of antidiabetic agents” and “sufficient amount of food,” and negatively associated with “early restoration of life-lines” and “sufficiency of sleep.” Thus, the glycemic control, associated factors and stress levels are altered in chronological order. Post-disaster diabetic medical care must consider these corresponding points in accordance with the time period.

Prediabetes Is Associated with Increased Long-Term Mortality Regardless of Subsequent Glycemic Progression

YU CHI WOI, CHI HO LEE, HI YIFONG, MAN YI YEUNG, KAREN S.L. LAM, HONG KONG, CHINA

Objective: To study the mortality risk in a long-term population-based prospective study among subjects with prediabetes (PreDM) at baseline, compared to those with persistent normal glucose tolerance (NGT), taking into account whether they had had non-persistent PreDM, persistent PreDM, or converted to diabetes, during the follow-up period.

Methods: Subjects without history of diabetes had oral glucose tolerance test (OGTT) performed at each visit. Those who attended the baseline visit (1995-6) and returned for assessment at least once in 2000-4, 2005-8 and 2010-2 were included. PreDM was defined as impaired fasting glucose (≥ 5.6 mmol/L) or impaired glucose tolerance (2 hour post-OGTT glucose ≥ 7.8 and <11.1 mmol/L). They were considered non-persistent PreDM, persistent PreDM or converted if they progressed to diabetes. Adjustments were age, family history of diabetes, smoking pack year, alcohol consumption, step count and BMI. We added logistic regression model. Adjustments were age, family history of diabetes, smoking pack year, alcohol consumption, step count and BMI. Adjustment was age, family history of diabetes, smoking pack year, alcohol consumption, step count and BMI. Adjustment was age, family history of diabetes, smoking pack year, alcohol consumption, step count and BMI. Adjustment was age, family history of diabetes, smoking pack year, alcohol consumption, step count and BMI.

Results: Among 1225 subjects, 629 with PreDM (non-persistent, 41.9%; persistent, 23.3%; converted, 34.6%), were included for analysis. Factors independently associated with PreDM at baseline were age, body mass index, dyslipidemia and physical inactivity, as analysed by logistic regression. After 21.8 (IQR: 21.4-22.3) years, there were 101 deaths. Age, smoking and PreDM were the independent predictors of death identified using backward multivariable Cox regression. The non-persistent, persistent and converted groups all had higher mortality risk compared to NGT (Hazard Ratio: 2.33, 2.47, 2.43, all p<0.05).

Conclusions: We concluded that PreDM increased long-term mortality, regardless of the subsequent mode of glycemic progression. Measures for smoking control and prevention of PreDM through promotion of healthy diet, regular exercise and weight control, are recommended.
1637-P

Fasting Plasma Mannose Level Is Associated with Insulin Sensitivity Independent of BMI in Japanese Individuals with Diabetes

ERI AMANO, SHIGO FUNAKOSHI, KUMIKO YOSHIMURA, SEIKI HIRANO, SATOKI DHMI, YOSHIO TERADA, SHIMPEI FUJIMOTO, Nankoku, Japan

Recently, integrated network analysis has revealed dysregulation in the metabolism of mannose, an epimer of glucose, in individuals with severe obesity who do not have significant diabetes. It was also found that fasting plasma mannose levels (M₀) are associated with insulin resistance independent of BMI. Since the association between mannose and insulin sensitivity (IS) in those with impaired glucose tolerance remains unknown, we aimed to investigate the association in individuals with varying degrees of glucose tolerance. Based on data of 75 OGTT in Japanese individuals without diabetic medication, individuals were classified as normal (NGT), impaired glucose tolerance (IGT), and diabetes (DM). In each group, 25 subjects were consecutively recruited (total 75 individuals, age 55±7 years; BMI: 24.9±3.8 kg/m²). Matsuda index (MI) was calculated as an index of IS. M₀ was assayed using HPLC. Normally-distributed log₁₀-transformed (ln-) values were used for MI and leptin. Although fasting plasma mannose (Glucose-like, HbA₁C, and ln-MI were significantly different among 3 groups, age, sex, BMI, and ln-MI were not different. In simple regression analysis, ln-MI was negatively correlated with BMI (NGT: r=-0.639, 1GT: r=-0.466, DM: r=-0.613) and ln-leptin (NGT: r=-0.480, IGT: r=-0.447, DM: r=-0.593) in all groups. Interestingly, although ln-MI was not significantly correlated with M₀ in NGT (r=0.241, P=0.245) and IGT (r=0.296, P=0.152), it was moderately and negatively correlated in DM (r=-0.626, P<0.001). In DM, ln-MI was slightly correlated with M₀ (r=0.484, P=0.014). In multiple regression analysis in DM, ln-MI was independently predicted by BMI (β=0.400) and M₀ (β=0.426), accounting for 51.2% (P<0.001) of the variability, which was larger than that in the prediction by BMI alone (37.6%). In conclusion, in our study, fasting plasma mannose was associated with insulin sensitivity independent of BMI in Japanese individuals with diabetes.

1638-P

Long-Term Survival in 200 Patients with Advanced Stage Colorectal Carcinoma and Diabetes Mellitus—A Single Institution Experience

NIKA SATEJ, NIKOLA BESIC, ANA PAVLIC, MILENA KERIN POVSIC, Ljubljana, Slovenia

Objective: Colorectal cancer surgery is often followed by postoperative complications which may impact survival. Diabetes mellitus (DM) and DM related comorbidities may initiate difficulties during cancer specific treatment and may have an impact on cancer management and outcome. The aim of our study was to find out if DM in patients with advanced colorectal carcinoma is associated with cancer-specific and overall survival.

Material and Methods: This study included 200 consecutive patients (131 males, 69 females, mean age 63 years) with elective colorectal cancer surgery at the Institute of Oncology Ljubljana from September 2010 to March 2013. Even 84% of patients had Stage 3 or 4 disease, so neo-adjuvant chemotherapy and/or radiotherapy were carried out in 59% of cases. DM was found in 32% (50/158) patients. Data about gender, age, body mass index, presence of DM, American Society of Anesthesiologists (ASA) physical status score, stage of disease and postoperative complications were collected prospectively. Univariate survival analysis was used to identify factors correlated with disease-specific and overall survival.

Results: Patients with DM had higher ASA score and BMI than those without DM. Rectum, colon and both of them were affected by cancer in 68%, 30% and 2% of cases, respectively. Stage 3 or 4 disease was found in patients with DM and without DM in 62% and 65%, respectively. Mean follow-up period was 47.5 years. Recurrence was diagnosed in 23% of patients with DM and in 25% of patients without DM. Altogether 41 patients died of cancer and 12 patients of other causes. Three-year cancer-specific survival in patients with DM and without DM was 85% and 89%, respectively (P=0.68). Three-year overall survival in patients with DM and without DM was 52% and 56%, respectively (P=0.63).

Conclusions: Presence of DM was not associated with tumor stage, disease-specific survival or overall survival in our group of patients with advanced colorectal carcinoma.

Supported By: Slovenian Research Agency

1640-P

Clinical Profile of Adults with Nonalcoholic Steatohepatitis (NASH) With and Without Type 2 Diabetes Mellitus (T2DM)

KENNETH CUSI, ALFRED S. BARRITT IV, VIRGINIA CLARK, ROBERTO J. FIRPI, SAMUEL KLEIN, ANNA LOK, ROHIT LOOMBA, LAURA MALAHAS, BRENT SCHWANDER-TETRI, CHERYL SCHOFEN, K. RAJENDER REDDY, JAWAHAR L. TAUNK, KATHLEEN WYNE, ARUN J. SANYAL, Gainesville, FL; Chapel Hill, NC; St. Louis, MO; Ann Arbor, MI; San Diego, CA; Philadelphia, PA; Palm Harbor, FL; Columbus, OH; Richmond, VA

Nonalcoholic Fatty Liver Disease (NAFLD), ranging from simple steatosis to its more severe form, steatohepatitis (NASH), is an increasingly common problem in patients with T2DM and is associated with progression to cirrhosis and extrahepatic complications (i.e., cardiovascular disease (CVD)). There is limited information on the clinical profile of T2DM patients with NASH in “real world” practice. Accordingly, we studied the clinical profile of participants (pts) with NASH and/or NASH cirrhosis (nonDM) and T2DM (NASH with T2DM or T2DNASH) in TARGET-NASH, a large longitudinal observational study of patients with NAFLD followed at 54 sites (39 academic/15 community) across the U.S. Data collected from medical records (including lab data, imaging, pathology, procedures, and outcomes) is sent to a central database utilizing novel data abstraction technology. Among 1743 pts studied to date in TARGET-NASH, 1261 had NASH diagnosed by biopsy or clinical criteria (699 T2DM and 562 nonDM). Pts with T2DM and NASH were older (median 61 vs. 56 years) and had a higher BMI than nonDM (34.0 vs. 32.0 kg/m², both p<0.001). The prevalence rates of hypertension (68 vs. 43%), dyslipidemia (42 vs. 25%), CVD (26 vs. 17%) all p<0.001, and cancer (17 vs. 12% p=0.015), were higher in T2DM compared to nonDM. Median ALT in T2DM was lower than nonDM (33 vs. 38 U/L, p<0.001). Among pts with a liver biopsy, advanced fibrosis was seen in 55% of T2DM vs. 35% nonDM, including 38 vs. 19% with cirrhosis, respectively (both p<0.001). Among pts with a biopsy and NAFLD Activity Score total, more T2DM had severe steatohepatitis than nonDM (38 vs. 23% p<0.001). In this large cohort of NASH pts managed in standard clinical practice, pts with T2DM had substantially different clinical profiles compared to nonDM. ALT, only modestly elevated in most pts with NASH, is not a reliable marker for NASH. Diagnosis requires reliance on clinical features and additional testing. Further investigation of independent risk factors and long-term outcomes is ongoing.
Impact of Early Intensification with Sitagliptin on Glycemic Goal Attainment among Patients with Metformin Monotherapy Failure
FLAVIA LJZYKOWICZ, JINAN LIU, SAMUEL S. ENGEL, SWAPNIL RAJPATHAK, North Wales, PA, Kenilworth, NJ

Background: Delay in the intensification of type 2 diabetes (T2DM) treatment after metformin monotherapy failure, or clinical inertia, is often observed among patients with poor glycemic control. Sitagliptin is used frequently as an add-on to metformin monotherapy among patients with T2DM. The objective of the study is to evaluate the association between early treatment intensification with sitagliptin and glycemic goal attainment among patients failing metformin monotherapy.

Methods: This retrospective database study of adult T2DM patients was conducted using the Quintiles Electronic Medical Record (EMR) database. The study population consisted of patients diagnosed with T2DM who failed to achieve A1C level of <7% on metformin monotherapy between January 2008 and June 2015. The study included two groups: 1) those who did not receive treatment intensification within 3 months after metformin failure (non-eary group), and 2) those who were intensified with sitagliptin within 3 months (early sitagliptin group). A Cox regression analysis was conducted to evaluate the association between sitagliptin use and A1C goal attainment within 12 months.

Results: We identified 2,852 patients aged ≥18 years with T2DM who failed metformin monotherapy, of which 262 patients were intensified with sitagliptin within 3 months and 2,490 patients were included in the non-eary group. A multivariate Cox regression model adjusted for age, gender, BMI, smoking status, baseline A1C, comorbidities, and other nondiabetic medications showed that early sitagliptin therapy resulted in doubling the likelihood of achieving A1C goal attainment (HR 2.12; 95% CI 1.80-2.50) within 12 months compared to non-eary group.

Conclusion: Early intensification with sitagliptin results in higher goal achievement levels among patients failing metformin monotherapy failure.

The Impact of Diabetes and Hyperglycemia in Patients Hospitalized for Dengue
ELVID D. BUENO COLMAN, SR., YESSIKA A. POZZO, GUILLERMO E. UMPIERREZ, Asuncion, Paraguay, Atlanta, GA, Alansun, Paraguay.

Dengue is a potentially lethal mosquito-borne flavivirus disease with about 300 million worldwide infections per year. We have experienced recurrent dengue epidemics in Brazil and Paraguay. We aimed to determine the impact and clinical outcome of diabetes (DM) and hyperglycemia during hospital admission in hospitalized patients for dengue. A total of 294 patients were admitted to a single medical center. Of them, 47% (19 patients) had the previous diagnosis of DM (age: 62±12 years, blood glucose [BG]: 238±116 mg/dl), 44 (14.9%) patients had hyperglycemia ([BG] ≥180 mg/dl) without a prior diagnosis of DM (49±18

1641-P

1642-P

1643-P

1644-P

1645-P
years. BG: 165±34 mg/dl and 214 (73%) had normoglycemia (49±18 years. BG: 110±18 mg/dl). Patients with diabetes and hyperglycemia were older and were more likely to present with severe or hemorrhagic dengue, hemodynamic shock, acute kidney injury (AKI) requiring admission to the ICU and blood transfusion, and longer length of stay. There was a single death in a non-CM patient. Compared to patients with normoglycemia, normo-DM patients with hyperglycemia (≥180 mg/dl) had more severe form of dengue with AKI (9.1% vs. 20.7%, OR: 2.61), hemodynamic shock (4.3% vs. 33.3%; OR: 2.61), ICU admission (4.3% vs. 33%, p<0.01) and longer length of hospital stay (47.7 days and 71.7 days, p<0.01).

Conclusion: Patients with DM and hyperglycemia were more likely to develop a more severe and hemorrhagic dengue compared to patients with normoglycemia. Because there is no specific dengue therapeutics, prevention is currently limited to vector control measures. A dengue vaccine program could represent a major advance in the control of the disease in patients with diabetes.

1646-P

Multiple Chronic Comorbidities in a T2DM Mediterranean Population

JOSEF FRANCH-NADAL, MANEL MATA-CASES, JORDI REAL, KARINE FERREIRA DE CAMPOS, MARTA CEDENILLA, ANTON GÓMEZ, DIDAC MAURICIO, BARCELONA, Spain, Madrid, Spain, Badalona, Spain, Spain.

Objective: T2DM patients often have multiple comorbidities which may impact patients’ management approach and treatment selection. This is the first study examining the co-prevalence of comorbidities such as CVD and CKD (GFR <60 ml/min and/or UACR ≥30 mg/g) across T2DM patients in Spain using a well-validated local database.

Methods: Retrospective cross-sectional study using the Spanish local electronic records DB “Information System for the Development of Research in Primary Care,” SIDIAP. Adult patients with T2DM were included and comorbid conditions were assessed using all medical records available from full years 2015-2016. Patient characteristics, laboratory measures and comorbidities were summarized via descriptive analyses, overall and by subgroups of age, gender and HbA1c levels.

Results: From 373,185 T2DM identified patients (overall population, OP), 55% were men, their mean age was 70 years, the mean T2DM duration was 9 years and the mean HbA1c value was 7.12% (SD 1.36). The most common comorbid conditions were hypertension (HTN): 72% of patients; hyperlipidemia (HL): 60%; obesity: 39%; CKD: 33% and CVD: 23%. The highest co-prevalence was the combination of HTN/HL (45.2%), followed by HTN/CKD (26.3%), HTN/CVD (18.8%) and CVD/HL (15.1%). CVD was more frequent in older groups (32.3% in patients ≥75 years-old) and in men (27.8% vs. 17.6%), while heart failure was more frequent in women (8.0% vs. 6.1%). CKD was found to increase with age, reaching 51.9% in patients ≥75 years. The coexistence of CKD and CVD in the whole population was 11.1%. Among T2DM patients with CVD and available GFR data (79,158, 91% of CVD patients), 57.6% had a GFR ≥60 ml/min (around 12% of OP), whereas 20.7% had GFR from 45 to <60, 14.2% had GFR from 30 to <45; 8.2% had GFR from 15 to <30/ml/min; and 1.3% had GFR <15/ml/min.

Conclusion: The frequency of comorbidities in T2DM patients from a Mediterranean area is high, and both age and gender play a role in overall comorbidity burden. CKD and CVD are frequent comorbid conditions among T2DM patients.

Supported By: Institut Universitari d’Investigació en Atenció Primària Jordi Gol. Merck Sharp & Dohme de España, S.A.

1647-P Diabetes Treatment in Patients with Renal Disease—How Many Are Receiving Contraindicated Drugs?

MANEL MATA-CASES, JOSEF FRANCH-NADAL, JORDI REAL, KARINE FERREIRA DE CAMPOS, MARTA CEDENILLA, ANTON GÓMEZ, DIDAC MAURICIO, BARCELONA, Spain, Madrid, Spain, Badalona, Spain.

Objective: To estimate the CKD (GFR <60 ml/min and/or UACR ≥30 mg/g) prevalence among T2DM patients and evaluate the use of antidiabetic drugs based on renal function.

Methods: Retrospective, cross-sectional study, analyzing data from the Spanish electronic records database: “Information System for the Development of Research in Primary Care,” SIDIAP, from Jan, 2015 to Dec, 2016. The use of antidiabetic drugs for each stage of chronic renal failure (CRF; GFR<60 mL/min) was evaluated in patients with available records of GFR. Furthermore, the adjusted RR for 5 events (global mortality, cardiovascular mor-tality, renal failure treated with dialysis or transplantation, acute renal failure and progression of kidney disease) according to KDIGO 2012 guidelines were assessed in those patients with available registers of both UACR and GFR.

Results: From the overall T2DM study population (373,185), 33% (122,296) had CKD, of those, 48% were women, with a mean age of 78 years, a mean T2DM duration of 11 years and a mean HbA1c value of 7.2% (SD 1.37). A total of 336,198 patients (90%) had GFR data, and 94,240 (28%) had CRF. Among those with GFR 30 << 45 ml/min (28,036, 8.9%), metformin was the most frequently used drug (48.6%), followed by insulin (33.5%), DPP-4i (21%) and sulfonylureas (15.9%). Among patients with GFR < 30 ml/min (13,262, 4%), insulin was the most used drug (50%), followed by DPP-4i (23%), metformin (16%), repaglinide (16%) and sulfonylureas (6.1%). The KDIGO 5 event-adjusted RR distribution among the 236,830 patients with available values of both UACR and GFR was: Low: 60.9%, Mild: 21.6%, High: 9.8% and Very high: 7.7%.

Conclusion: CKD is a very frequent comorbidity among T2DM patients. The use of antidiabetic drugs is more complex in these patients because many people with kidney disease are often elderly, and have long lasting disease and significant comorbidities. A relevant number of T2DM patients are still treated with contraindicated antidiabetic drugs regarding their renal function.

Supported By: Institut Universitari d’Investigació en Atenció Primària Jordi Gol. Merck Sharp & Dohme de España, S.A.

1649-P Burden of Hospitalization in Young-Onset Type 2 Diabetes—The Hong Kong Diabetes Register

CALVIN KE, ERIC S.H. LAU, ANDREIA LUK, RONALD C. MA, ALICE P. KONG, ELAINE CHOW, PHILIP M. CLARKE, JULIANA C. CHAN, TORONTO, ON, Canada, Hong Kong, China, Melbourne, Australia.

Objective: Young-onset type 2 diabetes (YOD, defined as age <40 years) is associated with early β-cell failure and poor risk factor control. While YOD incidence is increasing rapidly, its disease burden is poorly understood, resulting in clinical inertia and poor treatment adherence. We examined the burden of hospitalization among Chinese adults with YOD.

Supported By: ADA-Supported Research
Methods: We conducted a prospective cohort study measuring all-cause hospitalization in YOD and usual-onset type 2 diabetes (T2D) among adults aged 20-75 years using the Hong Kong Diabetes Register (2000-2015, n=21,779). We estimated the impacts of YOD and risk factor control on hospitalization rate after T2D diagnosis using negative binomial regression.

Results: YOD hospitalization had a bimodal distribution, with a disproportionate burden of mental illness < age 40 years (35.9% of bed-days; Figure 1). YOD was associated with a 3-fold increase in hospitalization rate vs. usual-onset T2D (adjusted rate ratio 2.8, 95% confidence interval 2.5-3.2). Intensified risk factor control (A1C<6.2%, blood pressure<120/75, LDL cholesterol<2.0 mmol/L) was associated with a 39.5% reduction in cumulative hospital days.

Conclusions: YOD is associated with substantial excess hospitalization across the adult lifespan. Urgent efforts are required to develop aggressive management strategies, and to address the unrecognized burden of mental illness in YOD.

Figure.

Support to University of Toronto, Chinese University of Hong Kong, Asia Diabetes Foundation

Diabetes Risk Behaviors Are Higher among Sexual Minority U.S. High School Students

LAUREN B. BEACH, BLAIR TURNER, GREGORY PHILLIPS II, Chicago, IL

Low physical activity (PA) and high sedentary behavior (SB) are associated with increased type 2 diabetes risk among youth. We investigated PA and SB among Youth Risk Behavior Survey (YRBS) respondents to determine if sexual minority youth may be at increased diabetes risk compared to heterosexual youth. Weighted city and state YRBS data were pooled across the adult lifespan. Urgent efforts are required to develop aggressive management strategies, and to address the unrecognized burden of mental illness in YOD.

Table 1.

<table>
<thead>
<tr>
<th>Sexual Identity</th>
<th>SB (95% CI) Hours/Day</th>
<th>PA (95% CI) Days/Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Female</td>
<td></td>
</tr>
<tr>
<td>Heterosexual</td>
<td>3.7 (3.7-3.8)</td>
<td>3.6 (3.6-3.7)</td>
</tr>
<tr>
<td>Gay/Lesbian</td>
<td>3.7 (3.4-4.0)</td>
<td>3.9 (3.9-4.2)</td>
</tr>
<tr>
<td>Bisexual</td>
<td>4.0 (3.7-4.3)</td>
<td>4.3 (4.1-4.4)</td>
</tr>
<tr>
<td>Unsure</td>
<td>4.0 (3.7-4.4)</td>
<td>4.3 (4.0-4.8)</td>
</tr>
</tbody>
</table>

Bold text: Unadjusted p-value Significant; *Adjusted p-value <0.001; Hetero-Reference.

Supported By: National Institutes of Health/National Institute on Alcohol Abuse and Alcoholism (R01AA024409 to G.P.)

Rate of Diabetes in Maricopa County, AZ

SHARON H. JAYCOX, SABINA PAGLIULUNA, Tempe, AZ

The prevalence of type 2 diabetes mellitus (T2DM) is well documented at the national, state, and even county level. Results are captured in the Behavior Risk Factor Surveillance System (BRFSS), a U.S. survey that collects data on disease rates and health-related risk behavior. The 2015 BRFSS audit revealed Arizona has an overall adult T2DM prevalence of 9.1%. Further, in Maricopa County, the region which includes the greater Phoenix area, the T2DM prevalence is higher at 10.8%. Conversely, there is limited data available on prediabetes rates in Maricopa County; therefore, we examined the rate of diabetes and prediabetes during community-partnered events as part of an educational “A1c initiative.” Basic demographic data as well as a fingerstick blood sample were obtained. HbA1c was measured with a hand-held monitor. 794 participants (272 men) were screened at 15 events from April 2016 to Sept 2017. The majority of participants were Hispanic descent (54%). HbA1c results were categorized according to the ADA guidelines: normal (< 5.7%), prediabetes (5.7-6.4%) and diabetes (≥6.5%) ranges. Mean HbA1c for all participants was 6.0% (±1.2), with 18% and 35% falling in the diabetes and prediabetes ranges respectively. Diabetes and prediabetes rates for males and females were similar. By ethnicity, prediabetes was highest among African Americans (AA) (41%), followed by white non-Hispanics (35%) then Hispanics (33%). Despite AA having a higher diabetes rate at 21%, HbA1c was significantly higher in Hispanics vs. AA diabetes only subjects (8.5% vs. 7.4% ±1.4, p<0.001), suggesting worse glycemic control for the Hispanic group. In line with the national average of prediabetes prevalence at 33.9%, the overall rate we observed was similar, yet higher in certain groups. Notably, the diabetes rate was nearly double than that of the BRFSS report. The initiative provided vital (pre)diabetes awareness to Maricopa County residents. These findings were shared with our community partners, to aid in developing strategies to best assist those at risk of developing T2DM.
**Presentation of Clinical and Characteristics of Patients with Maturity Onset Diabetes of the Young (MODY) at Women and Children’s Hospital of Buffalo**

Lina Saadeh, Lucy D. Mastrandrea, Buffalo, NY

Background: Maturity onset diabetes of the young (MODY) is a monogenic form of diabetes. It is rare, representing the fetal diagnosis in 1-2% of individuals with diabetes. In the pediatric cohort, it can be confused with type 1 diabetes. Clinical diagnosis is suspected in the case of hyperglycemia, lack of autoantibodies, and autosomal dominant transmission. This retrospective chart review evaluated the clinical presentation and characteristics of patients diagnosed with MODY by our practice with a goal of identifying patients that can be candidates for genetic testing.

Methods: Using ICD10 codes for MODY, we performed a retrospective chart review of patients carrying MODY diagnosis confirmed by genetic testing, who received their care at the Diabetes Center at Women and Children’s Hospital of Buffalo.

Results: We identified 10 subjects with confirmed genetic testing for MODY. Median age of presentation with hyperglycemia was 13.1 years (range of 3.6-17.3 years). Median HbA1c at presentation was 6.3% (range 6%-14%). While the initial referring diagnosis was elevated fasting BS (FBS) in 50% of subjects, FBS (mean 120±21 mg/dL) was abnormal for all but 1 subject at their first contact visit. All subjects had negative pancreatic autoantibodies. In our cohort, confirmatory testing was as follows: MODY2 (n = 6), MODY3 (n = 2), MODY4 (n = 1), and MODY5 (n = 1). Three subjects were assigned a MODY diagnosis prior to genetic testing. Two were siblings with family history of maternal MODY2. The third subject had a history of polyycistic kidney disease, sepsate uterus, and HbA1c in the prediabetes range. This subject was assigned a presumptive diagnosis of MODY 5 prior to genetic test.

Conclusion: In our practice, all subjects with confirmed MODY diagnosis had negative pancreatic autoantibodies with most meeting criteria for prediabetes diagnosis. Clinicians should have a high index of suspicion for MODY in subjects who do not fit criteria for T1DM or T2DM.

**Effects of Lifestyle Intervention on Metabolism Profile in People with Impaired Glucose Tolerance—The China Da Qing Diabetes Prevention Study**

Xin Qian, YanYan Chen, Hong-Mei Jia, Zhong-Mei Zou, GuiHong Gong, Yali An, Jiping Wang, Hui Li, Na Shi, Guangwei Li, Xin Qian, YanYan Chen, Hong-Mei Jia, Zhong-Mei Zou, GuiHong Gong

Aims: To investigate the effects of lifestyle intervention on metabolism profile in people with impaired glucose tolerance (IGT), and potential biomarkers for prevention of diabetes.

Methods: The study participants were identified as IGT by OGTT in 1986 and followed in 2006. Sixty participants were selected in the intervention group (I_Group) and 57 in control group (C_Group). UPLC-MS/MS analysis was performed by using the plasma samples. Principal component analysis and orthogonal partial least squares discriminant analysis were used for the data analysis.

Results: In 20-year follow-up study, I_Group had lower fasting plasma glucose, triglycerides and urine albumin/creatinine ratio comparing with C_Group. The metabolism profile was significant different between I_Group and C_Group, a total of 65 altered variables were obtained, and 9 metabolic pathways were changed, 4 pathways were considered as the most pertinent in the process of intervention: glyceroosphospholipid, arachidonic acid (AA) metabolism, glycerophospholipidynthesis (GPI)-anchor biosynthesis and vitamin B6 metabolism. In I_Group, after 6-year lifestyle intervention, 26 were still in IGT status and 24 change to diabetes after 20-year follow-up.

The metabolism profile was significant difference between development of diabetes and still in IGT subjects, a total of 53 altered metabolites were obtained. Compared with the 65 metabolites, 7 metabolites decreased after intervention but increased when they change to diabetes, 1 metabolite had opposite change tendency. The above 8 metabolites involved in 5 metabolic pathways: glyceroosphospholipid metabolism, GPI-anchor biosynthesis, linoleic acid, c-Linolemic acid, and AA metabolism.

Conclusions: The 65 metabolites and 4 metabolic pathways were changed after lifestyle intervention, 8 altered metabolites involved in 5 pathways were considered as the potential biomarkers related to diabetes outcome.

Supported By: Novo Nordisk/Chinese Academy of Sciences Research Fund; Novo Nordisk-Union Diabetes Research Talent Fund; Centers for Disease Control and Prevention; World Health Organization

**Association of Urinary Norepinephrine Levels with Increased Insulin Resistance in a General Population**

Masaya Murabayashi, Makoto Daimon, Hiroshi Murakami, Aya Kamba, Satoru Mizushima, Hiissaki, Japan, Nachinohe, Japan

Since activation of the sympathetic nervous system is associated with both impaired insulin secretion and insulin resistance, or namely with diabete, evaluation of such action in ordinary clinical settings appears to be important. Urinary levels of catecholamine metabolite, norepinephrine (NE) may be such a marker. Therefore, we here examined association of urinary NE levels with urinary insulin secretion and resistance evaluated by HOMA indices in a general population. From 1,149 participants of the 2016 population-based Iwaki study of Japanese, 1,037 individuals with fasting blood glucose levels, 64-140 to assess HOMA indices precisely were enrolled in the study (gender (M/F): 407/630; age: 53.4±15.5). The Iwaki study is a health promotion study of people over 20 years old to prevent lifestyle-related diseases and prolong their lifespans, and, the participants were those who believe themselves as healthy. Their urinary NE levels were 0.20±0.08 mg/mgCr. Univarient linear regression analyses showed a significant association of urinary NE levels with HOMA-R (β=0.1506, p<0.0001) and HOMA-β (β=0.1254, p<0.0001). Adjustment with age, gender, and multiple factors correlated with HOMA indices (Body mass index, triglyceride, Hypertension, %fat, HbA1c) showed a significant association with HOMA-R (β=0.1167, p=0.0012) but not with HOMA-β (β=0.0117, p=0.762). Further, analysis with subjects stratified into 2 groups (risk and non-risk) using the cut-off value of NE to predict insulin resistance (HOMA-R>1.6) determined by ROC analysis (0.215 mg/mgCr) showed that those at risk had an OR of 2.38 (CI: 1.49-3.74) after adjustment for the factors listed above. Increased urinary NE levels seem to be a marker for insulin resistance, or namely risk for diabetes in general.
Prevalence of Prediabetes and Undiagnosed Diabetes among Adults Aged 18 to 70 Years in France—The CONSTATNES Cohort
SONSOLES FUENTES, SANDRINE FOSSE-EDORH, NOLWENN REGNAULT, MARCEL GOLDBERG, EMANNOUEL COSSON, Paris, France, Saint Maurice, France, Villejuif, France, Bondy, France

Introduction: This study aimed to update the prevalence of different diabetes stages in France among adults aged 18 to 70 years according to gender, age and socioeconomic status.

Methods: The CONSTATNES cohort is a randomly selected representative sample of French adults. In 2013, 16,340 participants were recruited. Based on data from self-administered questionnaires, medical examination (including fasting plasma glucose (FPG) measurement) and data from the French National Insurance System (antidiabetic drugs consumption and hospitalization), three stages were defined: prediabetes (WHO definition), diagnosed and undiagnosed (FPG ≥ 126 mg/dL) diabetes. Weighted prevalence of each stage was estimated for all population and by gender, age and education. Confidence intervals were calculated using logit transformation.

Results: In 2013, the prevalence of prediabetes, undiagnosed diabetes and diagnosed diabetes was 7.4%, 1.9% and 3.9%, respectively. All these rates were higher in males, increased steadily with age while decreasing with education (Figure).

Discussion: Our results show that the prevalence of prediabetes and unknown diabetes are still very high in developed countries, like France. They highlight the need to increase primary prevention, and to reinforce secondary prevention of diabetes, especially through promotion of screening in population at risk.

1658-P

Conformance to Type 2 Diabetes (T2D) Guidelines in a Large U.S. Health Plan
RAJESH MEHTA, ALISON EDWARDS, SWAPNIL RAJPATHAK, AJAY SHARMA, Health Plan

Trends in Type 2 Diabetes Mellitus Complications, Drug Utilization, and Laboratory Outcomes, 2012-2017
RADIKA NAIR, ZHENHAI ZHAO, PRANAV GANDHI, YONG LI, KIMBERLY BRODOVICZ, YUNUS A. MEAH, SAMANEH KALIRAI, CHAD MORETZ, MICHELE MACKENZIE, BRADLEY CURTIS, TODD G. PREWITT, Louisville, KY, Indianapolis, IN, Ridgefield, CT, Sydney, Australia

Impact of Diabetes on Colorectal Cancer Screening Rates in U.S. Adults
JENNIFER A. CAMPBELL, REBEKAH J. WALKER, CHRISTIAN EILER, LEONARD E. EGEEDE, Milwaukee, WI

Background: Individuals with diabetes have an increased risk for colorectal cancer, however routine diabetes care visits may increase colorectal screening rates. The aim of this study is to examine whether diabetes diagnosis influences screening completion in U.S. adults.

Methods: This study used data from 464,684 adults completing the 2014 BRFSS national survey. Logistic regression models tested the likelihood of glucose-lowering medications, glycemic control remained suboptimal, with increasing prevalence of complications such as kidney disease in both prevalent and incident cohorts as patients progressed through their diabetes.

Table.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Era 1</th>
<th>Era 2</th>
<th>Era 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>% No HC 2.5%</td>
<td>2.7</td>
<td>2.9</td>
<td>3.7</td>
</tr>
<tr>
<td>% No HC 4%</td>
<td>2.8</td>
<td>3.0</td>
<td>4.0</td>
</tr>
<tr>
<td>% No HC 6%</td>
<td>3.1</td>
<td>3.3</td>
<td>5.0</td>
</tr>
<tr>
<td>% No HC 8%</td>
<td>3.2</td>
<td>3.5</td>
<td>5.3</td>
</tr>
<tr>
<td>% No HC 10%</td>
<td>3.4</td>
<td>3.7</td>
<td>5.4</td>
</tr>
</tbody>
</table>

Supported By: Boehringer Ingelheim; Eli Lilly and Company

Impact of Diabetes on Colorectal Cancer Screening Rates in U.S. Adults
JENNIFER A. CAMPBELL, REBEKAH J. WALKER, CHRISTIAN EILER, LEONARD E. EGEEDE, Milwaukee, WI

Background: Individuals with diabetes have an increased risk for colorectal cancer, however routine diabetes care visits may increase colorectal screening rates. The aim of this study is to examine whether diabetes diagnosis influences screening completion in U.S. adults.

Methods: This study used data from 464,684 adults completing the 2014 BRFSS national survey. Logistic regression models tested the likelihood of colorectal screening by diabetes status, and whether diabetes quality of care indicators predicted colorectal screening among diabetes patients. A stratified analysis examined predictors of screening by demographic status for diabetes/nondiabetes patients.
Epidemiology/Genetics
POSTERS

1661-P
Metabolic Function in 5,047 Adults with Type 2 Diabetes on Metformin Alone Based on Oral Glucose Tolerance Test (OGTT) Data from the GRADE Cohort
KRISTINA UITZSCHNEIDER, MARY ANN BANERJI, JOSHUA I. BARZILAY, ERICA V. GONZALEZ, PARMARARZ ISMAIL-BEGI, KIEREN J. MATHER, PHILIP RASKIN, NAJI YOUNGS, STEVEN E. KAHN, GRADE RESEARCH GROUP, Seattle, WA, Brooklyn, NY, Duluth, GA, Houston, TX, Shaker Heights, OH, Indianapolis, IN, Dallas, TX, Rockville, MD, Washington, DC. 

Little data exist on the relationship between glycemic variables, insulin sensitivity and insulin and C-peptide responses in subjects with T2DM. We assessed these relationships using baseline OGTT data from the Glucose Reduction Approaches in Diabetes, A Comparative Effectiveness study (GRADE) cohort. Eligibility included T2DM <10 years, HbA1c 6.8-8.5% treated with metformin alone, glucose, insulin and C-peptide were measured at 0, 15, 30, 60, 90 and 120 minutes in 5,047 OGTTs. Insulin sensitivity was measured by HOMA-S and insulin and C-peptide responses were estimated using HOMA-IR and incremental area under the curve (incAUC) hormone/glucose0-120. Subjects were 63.6% men, 57.2±10 years old (mean±SD), with HbA1c 7.5±0.5% and T2DM duration 4.2±2.8 years. Insulin and C-peptide responses were inversely associated with HOMA-S in a curvilinear manner (p<0.001 for all). Glycemic variables were all inversely associated with HOMA-S and insulin and C-peptide responses (Table, p<0.001 for all). The weakest association was between HbA1c and HOMA-S and the strongest between 2h glucose and incAUC C-peptide. Even in established diabetes there is measurable β-cell function and these measures remain proportional to glycemic responses. We plan to use these baseline measures of β-cell function as potential determinants of treatment outcomes in GRADE.

Table. Adjusted Regression Data. 

<table>
<thead>
<tr>
<th></th>
<th>HOMA-S</th>
<th>ΔG0-30</th>
<th>ΔG0-120</th>
<th>incAUC G0-30</th>
<th>incAUC CP/G0-120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose</td>
<td>0.28</td>
<td>-0.20</td>
<td>-0.21</td>
<td>-0.28</td>
<td>-0.32</td>
</tr>
<tr>
<td>2h glucose</td>
<td>0.18</td>
<td>0.25</td>
<td>0.27</td>
<td>0.34</td>
<td>0.44</td>
</tr>
<tr>
<td>incAUC G0-120</td>
<td>0.10</td>
<td>-0.16</td>
<td>-0.16</td>
<td>-0.18</td>
<td>-0.18</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.07</td>
<td>-0.10</td>
<td>-0.09</td>
<td>-0.13</td>
<td>-0.15</td>
</tr>
</tbody>
</table>

Regression models are presented as signed R² adjusted for sex, age, race, BMI, T2DM duration, eGFR and metformin dose. = insulin, G = glucose, CP = C-peptide.

Supported By: National Institute of Diabetes and Digestive and Kidney Diseases

1662-P
Evaluating the Combination of Metabolic Syndrome and Different Body Mass Index Categories to Predict Risk for Mortality among U.S. Adults
TING HUAI SHI, SUNDAR NATARAJAN, New York, NY. 

Body Mass Index (BMI) categories alone do not necessarily predict negative outcomes. We examined if further stratification based on metabolic syndrome (MetS) provides additional value in predicting mortality. We analyzed population-based data from adults in the National Health and Nutrition Examination Survey from 1999-2010. BMI categories (in kg/m²) were: normal (19.5-25.0), overweight (25.1-30.0) and obese (>30.0). Normal BMI participants without MetS served as the reference group. After initial unadjusted analyses we performed Cox proportional hazards models controlling for age, gender, race-ethnicity, education, income and smoking. We included 12,048 participants. Unadjusted mortality curves (Figure) show that the normal MetS group had the highest mortality rate, followed by overweight MetS, which in turn is significantly higher than obese MetS. All the no MetS groups had significantly lower mortality than their MetS counterparts. Adjusted Cox regression showed that only the normal MetS (HR 1.7, CI 1.2-2.4) and obese MetS group (HR 1.3, CI 1.1-1.6) had higher hazard rates than the reference group. Metabolic syndrome and obesity categories provide significant additional prediction of mortality. Normal weight subjects with MetS have the highest mortality, in contrast to previous studies. Treatment strategies should incorporate MetS and obesity.

Figure.

Table. Parameter Estimates for Cox Proportional Hazards Models of Mortality (log-likelihood 8861.2, p-value 0.0002). 

<table>
<thead>
<tr>
<th>Species</th>
<th>Baseline insulin</th>
<th>Follow-up insulin</th>
<th>Baseline MetS</th>
<th>Follow-up MetS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cer-16:0</td>
<td>1.13 (0.71-2.00)</td>
<td>1.10 (0.61-1.91)</td>
<td>1.15 (1.08-1.22)</td>
<td>1.11 (1.01-1.22)</td>
<td>0.03</td>
</tr>
<tr>
<td>Cer-18:0</td>
<td>1.11 (0.86-1.51)</td>
<td>1.12 (0.86-1.49)</td>
<td>1.12 (1.10-1.17)</td>
<td>1.13 (1.04-1.20)</td>
<td>0.002</td>
</tr>
<tr>
<td>Cer-20:0</td>
<td>1.12 (0.71-1.76)</td>
<td>1.10 (0.93-1.28)</td>
<td>1.13 (1.08-1.82)</td>
<td>1.11 (1.09-1.19)</td>
<td>0.002</td>
</tr>
<tr>
<td>Cer-22:0</td>
<td>1.13 (0.86-1.19)</td>
<td>1.12 (0.89-1.28)</td>
<td>1.15 (1.08-1.21)</td>
<td>1.13 (1.04-1.22)</td>
<td>0.002</td>
</tr>
<tr>
<td>Cer-24:0</td>
<td>1.05 (0.89-1.19)</td>
<td>1.09 (0.84-1.42)</td>
<td>1.06 (1.00-1.13)</td>
<td>1.11 (1.01-1.21)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Covariates: age, sex, site, education, smoking, log (BMI), waist, physical activity.

Supported By: National Institute of Diabetes and Digestive and Kidney Diseases
ANTIPLATELET THERAPY AS A PRIMARY PREVENTION STRATEGY FOR CARDIOVASCULAR RISK. The American diabetes association (ADA) standards of medical care in diabetes 2017 recommends considering aspirin therapy as a primary prevention strategy for patients with type 2 diabetes who are at increased cardiovascular risk. The aim of this study was to investigate the prescription rate of antplatelet as a primary prevention treatment in diabetes patients in Taiwan.

Methods: We conducted a new user cohort from the Taiwan longitudinal cohort of diabetes patients (CLCP) between 1999 and 2013 in diabetes patients aged over 20. We stratified these patients into three risk groups (low, intermediate, and high risk) according to the standards of medical care in diabetes 2017 to explore the utilization of antplatelet agent as a primary prevention strategy in each risk stratification.

Results: We assembled a diabetic cohort (n=513,012) who were potentially eligible for primary prevention therapy. We then stratified them into low (n=27,572), intermediate (n=190,038) and high (n=295,402) cardiovascular risk. Around 1% of patients in the low-risk group were dispensed antplatelet agents, 8% in the intermediate-risk group, and about 16% in the high-risk groups. The median dispensing days for total follow-up period in those with low risk was 189 days, equally 12% of the period from initiating antplatelet agents to study end. The median dispensing days for those with high risk was 392 days, about one-fourth of the period from starting antplatelet agents to study end.

Conclusions: Aspirin or alternative effective antplatelet agents as a primary prevention strategy for type 2 diabetes patients with increased cardiovascular risks were underutilized in Taiwan.
1668-P
Type 2 Diabetes Remission—Analysis of Three Population-Level Historical Cohorts
SRIKANTH TANGELLOJU, GIANG VU, HUNTER CHAVIS-BLAKELY, BERT B. LITTLE, Louisville, KY
Objective: To analyze the characteristics of individuals who went into remission for type 2 diabetes mellitus (T2DM) in the absence of bariatric surgery in three large population level datasets.

Methods: Data from three large T2DM cohorts were used in this analysis: a) 10,059 subjects from a longitudinal Medicare cohort (n=2.4 Million); b) 4,967 subjects, Continuous NHANES (n=82,091); and c) 562 subjects, NHANES III (n=33,994). A Medicare T2DM individual with no T2DM related claims continuously for more than 12 months was considered to be in remission. In the NHANES data T2DM remission was defined as an HbA1c ≤ 5.7 without T2DM related medications. Cox proportional hazards was used to identify significant variables associated with T2DM "remission" in the Medicare data. NHANES data were analyzed with multiple logistic regression with T2DM remission as the dependent variable.

Results: In the Medicare dataset 4.97% met the criteria for T2DM remission in a five-year longitudinal study, while 2.76% and 1.97% of the continuous NHANES and the NHANES III subjects, respectively, achieved remission in the cross-sectional cohorts. The factors associated with T2DM remission were no statin use; no insulin use; no hypertension; no hyperlipidemia; no neuropathy; no retinopathy; female gender; non-African American ethnicity; decreased waist circumference and lower systolic blood pressure (Bonferroni adjusted p<0.05). The rate of T2DM remission appears to be approximately 1.97 to 4.97%.

Conclusions: T2DM remission triggers exist (Lancet, Dec 2017). Of the factors associated with T2DM remission, only ethnicity and gender are non-modifiable risk factors. Therefore, diabetes prevention and management programs should concentrate on lowering body weight, lipids, and blood pressure. Management of these factors is associated with T2DM remission. Identification of other factors associated with T2DM maY lead to more efficacious programmatic management of the disease and attenuation of serious co-morbidities.

Supported By: University of Louisville

1669-P
The Number of Metabolic Syndrome Components and Incidence Rates of Type 2 Diabetes—A Korean National Sample Cohort Study
MIN-KYUNG LEE, HYUK-SANG KWON, Gyeonggi, Republic of Korea, Seoul, Republic of Korea
Background: Metabolic syndrome (MetS) is associated with an increased risk of diabetes. In this study, we aimed to investigate the incidence rate of type 2 diabetes according to the number of MetS components using data from the Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC).

Methods: A total of 24,582,108, aged 20 years or older, with no history of diabetes were recruited between 2009 and 2012. MetS components were defined using the modified criteria of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III). Type 2 diabetes was defined as a current medication history of antidiabetic drugs and the presence of International Diabetes Federation criteria. Type 2 diabetes was defined as an HbA1c ≥ 6.5% in the NHANES data and as having diabetes at a mean age of 76.5 years. Higher serum γ-GT was associated with increased risk of diabetes (HR=1.22, 95% CI=1.20-1.24), and had a strong positive association with early onset diabetes (HR=1.32, 95% CI=1.24-1.40). An additive impact of higher γ-GT on dementia was observed regardless of glycemic status, and prevalent diabetes with the highest γ-GT quartile had a 1.8-fold increased risk of diabetes (HR=1.82, 95% CI=1.78-1.85). This effect of γ-GT concentration in diabetes was more prominent in individuals with vascular dementia (HR=1.94, 95% CI=1.84-2.04).

In conclusion, γ-GT concentration as well as glycemic status could be a future risk factor for dementia in the general population.

1670-P
Gamma Glutamyltransferase and Risk of Dementia in Normal, Prediabetes, and Diabetes Populations—A Nationwide Cohort Study with 6.5 Million People
EUGENE HAN, MINYOUNG LEE, YONGIN CHO, CHUL WOO AHN, BONG-SOO CHA, YONG-HO LEE, Daegu, Republic of Korea, Seoul, Republic of Korea
Diabetes is associated with cognitive impairment and increases risk of dementia, but until now the role of gamma-glutamyltransferase (γ-GT) in dementia has not been studied. We thus investigated the impacts of γ-GT and glycemic status on incident dementia in a nationwide sample. We determined incident dementia including Alzheimer’s disease and vascular dementia, analyzing data from participants aged 40 years or older in the National Health Insurance Database, collected by the National Health Insurance Service in Korea, from January 2009 to December 2015. During a median follow-up of 7.6 years, 727,857 participants (5.4%) were diagnosed as having dementia at a mean age of 76.5 years. Higher serum γ-GT was associated with increased risk of dementia (HR=1.22, 95% CI=1.20-1.24), and had a strong positive association with early onset diabetes (HR=1.32, 95% CI=1.24-1.40). An additive impact of higher γ-GT on dementia was observed regardless of glycemic status, and prevalent diabetes with the highest γ-GT quartile had a 1.8-fold increased risk of diabetes (HR=1.82, 95% CI=1.78-1.85).

In conclusion, γ-GT concentration as well as glycemic status could be a future risk factor for dementia in the general population.

1671-P
Nationwide Analysis of Excess Deaths attributable to Diabetes in Brazil
PAULA BRACCO, EDWARD W. GREGG, DEBORAH B. ROLKA, MARIA J. SCHMIDT, SANDHI MARIA BARRETO, PAULO A. LOTUFO, ENIRTES C. MELO, BRUCE B. DUNCAN, Porto Alegre, Brazil, Atlanta, GA, Belo Horizonte, Brazil, Sao Paulo, Brazil, Rio de Janeiro, Brazil
Background: Little is known about the magnitude of excess mortality due to diabetes in low and middle income countries. Brazilian data to that end have been limited by reliance on death certificates and their subjective assignment of diabetes as a cause of death. We provide estimates of excess mortality due to diabetes by combining mortality risks from the ELSA-Brazil cohort with nationally representative surveys and databases.

Methods: We calculated the standardized mortality rate ratio for those with (vs. without) self-reported diabetes in ELSA-Brazil by Poisson regression adjusting for age, sex, race and education. We obtained similarly adjusted, self-reported diabetes prevalence from the 2013 National Health Survey. Mortality and population projections were from national statistics. We combined these data to model the excess deaths due to diabetes.

Results: In 2013, among adults with diabetes aged 35 to 74 (Table), 73,092 deaths (13% of total) could have been avoided if the mortality rate in people with diabetes were the same as in those without diabetes. The percent ranged from 5.9% in persons aged 35-49 to more than 16% in those 60 or older. In the national mortality system, only 31,117 deaths (13% of total) could have been avoided if the mortality rate in people with diabetes were the same as in those without diabetes. Brazilian data to that end have been limited by reliance on death certificates and their subjective assignment of diabetes as a cause of death. We provide estimates of excess mortality due to diabetes by combining mortality risks from the ELSA-Brazil cohort with nationally representative surveys and databases.

Table:

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Standardized Mortality Rate Ratio</th>
<th>Population</th>
<th>Total Deaths</th>
<th>Deaths among People with Diabetes</th>
<th>Excess Deaths Associated with Self-Reported Diabetes %</th>
<th>% of Total Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-44</td>
<td>2.40</td>
<td>746,790</td>
<td>19,586,124</td>
<td>10,200</td>
<td>11,722</td>
<td>4,678</td>
</tr>
<tr>
<td>45-59</td>
<td>1.70</td>
<td>942,978</td>
<td>8,791,256</td>
<td>140,577</td>
<td>30,860</td>
<td>12,194</td>
</tr>
<tr>
<td>60-64</td>
<td>1.35</td>
<td>941,915</td>
<td>4,953,378</td>
<td>182,450</td>
<td>59,787</td>
<td>25,199</td>
</tr>
<tr>
<td>65-74</td>
<td>1.35</td>
<td>1,333,776</td>
<td>106,697</td>
<td>35,565</td>
<td>40,032</td>
<td>17,473</td>
</tr>
<tr>
<td>Total</td>
<td>1.91</td>
<td>3,020,252</td>
<td>34,506,004</td>
<td>549,864</td>
<td>33,504</td>
<td>70,092</td>
</tr>
</tbody>
</table>

Supported By: Ministry of Science, Technology, Innovation and Communication of Brazil
Subjective Sleep Debt Is Correlated with Body Fat Percentage Independent of Sleep Duration

XIAO YAN, CHRISTIAN BENEDICT, Uppsala, Sweden

No study has investigated whether subjective sleep debt (i.e., the gap between self estimations of sleep duration and sleep requirement) is linked to body fat mass. We studied 20,531 Swedish adults aged between 35 and 78 years (mean age: 60.9 ± 8.5 years, 56.8% women). Self-reported sleep duration and sleep needed for feeling fully rested (both in hours/day) were obtained by questionnaire. Subjective sleep debt per day was calculated by subtracting the value of sleep requirement with sleep duration. Fat mass was estimated by bioelectrical impedance analysis. Body fat percentage was calculated based on fat mass (kg) per total body mass (kg). Analysis of covariance (adjusting for age, gender, and self-reported sleep duration) was utilized to test the body fat percentage differences between hours of sleep debt, followed by Bonferroni corrections for multiple comparisons. Compared to those without subjective sleep debt, adults reporting a sleep debt of 2 hours and 3 hours or more were respectively associated with a 0.9 (95% CI: 0.5, 1.3) and 2.2 (95% CI: 1.4, 3.1) higher percentage of body fat mass (both p < 0.001). The corresponding differences when comparing these two groups to those reporting 1-hour sleep debt were 1.4 (95% CI: 1.0, 1.8) and 2.7 (95% CI: 1.9, 3.5), (both p < 0.001). The results suggest that subjective sleep debt of greater than one hour per day is associated with significantly higher body fat percentage.

Table.

Subjective sleep debt | Body fat percentage
--- | ---
0 hour | 
1 hour | 
3 hours or more | 

Supported By: Åke Wiberg Foundation (M17-0088); Fredrik and Ingrid Thuring Foundation (2017-00313)
Epidemiology—Other

1676-P
Diabetes Prevalence in North America and Caribbean Region in 2017 and 2045
YADI HUANG, SUVI KARURANDA, EDWARD J. BOYKO, BELMA MALANDA, Brussel, Belgium, Uccle, Belgium, Seattle, WA

Aims and Objectives: Diabetes is a serious and increasing global epidemic, and accurate estimates are essential for more efficient allocation of resources. The International Diabetes Federation (IDF) North America and Caribbean Region (NAC) consist of the U.S.A, Mexico and Canada, as well as 25 Caribbean countries and territories. The new edition of the International Diabetes Federation (IDF) Atlas (IDF, 2017) provides estimates of the number of people (18-99 years) living with diabetes in the IDF North America and Caribbean (NAC) Region.

Methodology: Estimates for diabetes in adults were taken from 24 data sources in the IDF NAC region, representing 14 out of 28 countries. Selected characteristics of these data sources are as follows: Barbados, Mexico, Suriname, Trinidad and Tobago and the U.S. had studies conducted within the last five years; Belize, Haiti, Mexico and the U.S. Virgin Islands had studies that performed oral glucose tolerance tests. Prevalence rates for other countries may be underestimated due to limited data sources on oral glucose tolerance test. The details of the methodology were described in IDI Diabetes Atlas 8th Ed.

Results and Conclusion: Approximately 50.1 (41.8-56.1) million people or 13.1% (10.9-14.6%) of adults aged 18-99, are living with diabetes in the IDF NAC region in 2017. The age-adjusted prevalence is 10.8%, which is highest among all seven IDF regions. If the trend continues, the number of people with diabetes is projected to reach 73.4 (58.8-83.4) million in 2045. About 37.6% of those people living with diabetes in this region are estimated to be undiagnosed in 2017. The number of deaths attributed to diabetes from age 20 to 99 years is 378,720 in 2017. The total healthcare expenditure related to diabetes in NAC region is USD 439,858 million in 2017 and will reach USD 508,315 million by 2045. Diabetes exerts a heavy burden in this region. Therefore effective diabetes prevention and management programs should be implemented in order to control diabetes prevalence.

1677-P
Seasonal Trends in HbA1c Level in Adult Patients with Type 1 Diabetes Treated with Personal Insulin Pumps
BARTOMIEJ MATEJKO, BEATA KIEC-WILK, SANDRA MROZINSKA, TOMASZ KLIWA, MACKIJE MALECKI, Koszalin, Poland

Introduction/Aim: The DCCT and other studies showed that the variability in HbA1c in adult patients with type 1 diabetes treated with personal insulin pumps. HbA1c was measured at a tertiary care university hospital on the Bio-Rad D10 hemoglobin testing system. Differences between groups (12 groups for 12 months and 6 for every consecutive two months) were assessed using the Kruskal-Wallis and post-hoc tests.

Results: Patients median age was 24 years [range 18-80 years], median BMI 22.9 kg/m² [15.6-43.7 kg/m²], median diabetes duration 12 [1-40 years] and median duration on personal insulin pump 6 [0-18 years]. A total of 1,438 HbA1c measurements were analyzed. Median HbA1c level for the whole study period was 7.25% [55.7 mmol/mol] (range 4.8-12.8% [29-116.4 mmol/mol]). There were seasonal differences in HbA1c over 12 months for the whole study period was 7.25% [55.7 mmol/mol] (range 4.8-12.8% [29-116.4 mmol/mol]). There were some earlier reports showing a seasonal variability in the HbA1c level in a pediatric population. There were some earlier reports showing a seasonal variability in the HbA1c level in a pediatric population.

[Methods: We evaluated seasonal HbA1c changes over a period of 9 years (2009-2017) in 453 adults with type 1 diabetes (T1DM) treated with personal insulin pumps. HbA1c was measured at a tertiary care university hospital on the Bio-Rad D10 hemoglobin testing system. Differences between groups (12 groups for 12 months and 6 for every consecutive two months) were assessed using the Kruskal-Wallis and post-hoc tests.

Results: Patients median age was 24 years [range 18-80 years], median BMI 22.9 kg/m² [15.6-43.7 kg/m²], median diabetes duration 12 [1-40 years] and median duration on personal insulin pump 6 [0-18 years]. A total of 1,438 HbA1c measurements were analyzed. Median HbA1c level for the whole study period was 7.25% [55.7 mmol/mol] (range 4.8-12.8% [29-116.4 mmol/mol]). There were seasonal differences in HbA1c over 12 months (p<0.02). The lowest HbA1c was observed in summer (July, 6.8% [50.8 mmol/ mol]) and the highest in winter months (from 7.1% [54.1 mmol/mol] in January to 7.3% [56.3 mmol/mol] in February). HbA1c was lower in July than in February (p<0.03). After combining two consecutive months in one group seasonality of HbA1c values was still observed (p<0.008). Median HbA1c in July/August (6.9% [51.9 mmol/mol]) was lower than in January/February (7.2% [55.2 mmol/mol], p<0.01) and in November/December groups (7.3% [56.3 mmol/mol], p<0.02).

Conclusion: To our knowledge this is the first report concerning HbA1c seasonal fluctuations in well controlled cohort of adult T1DM patients treated with insulin pumps. Seasonal changes of HbA1c levels (peak in summer months, drop in winter months) in such a group of patients should be considered in patient education and diabetes management.

1678-P
Population-Level Burden of Diabetes by Leisure, Transportation, and Work-Based Physical Activity—NIHANES, 2011-16
SANDRA ECHEVERRIA, ANNA A. DIVNEY, EMMA K. TSUI, CHLOE MIRZAYI, New York, NY

Introduction: An abundance of evidence has shown that leisure-time physical activity (PA) is associated with reduced risk of diabetes. Adults, however, engage in various forms of PA, with potentially differential health effects. We tested if specific modes of PA are differentially associated with diabetes prevalence in a population-based adult sample.

Methods: Among 18,903 racially/ethnically diverse adults ≥20 years old participating in NIHANES 2011-16, we fit separate log binomial models to test associations between mode of PA and diabetes, and whether associations differed by race/ethnicity. Participants completed none, some (1-149 min/week) or met national PA guidelines (150+ min/week) for leisure time, work, transportation and combined motor (‘AP’). Diabetes was based on laboratory-confirmed HbA1C ≥ 6.5% or ever being told by a health professional respondent had diabetes.

Results: For each mode of PA and All modes combined, respondents completing ≥150+ minutes of PA were 33% to 39% less likely to have diabetes than respondents who completed no PA, even after controlling for covariates. There was a general gradient of decreasing prevalence with increasing PA. Effects varied by race/ethnicity for all PA modes except work-based PA (P<0.01).

Conclusions: Meeting PA guidelines via any mode appears to confer protection from diabetes, but there are differential effects by mode and race/ethnicity.

Table.

<table>
<thead>
<tr>
<th>Model</th>
<th>Leisure Time Physical Activity</th>
<th>Transportation Physical Activity</th>
<th>Work-Based Physical Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>Male n=15,744</td>
<td>Male n=11,256</td>
<td>Male n=15,744</td>
</tr>
<tr>
<td>Model 2</td>
<td>Female n=11,400</td>
<td>Female n=10,036</td>
<td>Female n=11,400</td>
</tr>
<tr>
<td>Model 3</td>
<td>Male n=15,744</td>
<td>Male n=11,256</td>
<td>Male n=15,744</td>
</tr>
<tr>
<td>Model 4</td>
<td>Female n=11,400</td>
<td>Female n=10,036</td>
<td>Female n=11,400</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; PA, prevalence ratio; aPR, adjusted prevalence ratio.

Supported By: Centers for Disease Control and Prevention (U48DP005008), Professional Staff Congress/City University of New York

1679-P
PETER P. TOTH, MICHAEL PALMER, Sterling, IL, Manchester, United Kingdom

Obesity is associated with increased CV risk. Using data from National Health and Nutrition Examination Surveys (NIHANES, 2003-2012), we estimated frequency and prevalence of obesity in U.S. adults (≥20 years).

Participants in 5 NIHANES surveys with fasting blood serum data (n=11,256) were pooled and categorized as overweight, obese, or morbidly obese (BMI 25-29.9, 30-39.9, ≥40 kg/m², respectively). Results are stratified by age, sex, and ethnicity. Extrapolations to the U.S. adult population were performed using the direct method to the 2011-2012 U.S. Census. Proportion of U.S. adults categorized as overweight is high, irrespective of age, sex, or ethnicity (Table). Obesity prevalence is high in adults aged 20-39 years (30% of men and 33% of women) and those aged ≥60 years (35% of men and 38% of women). In men, obesity/morbid obesity prevalence is similar between ethnic groups. However, non-Hispanic black women have a higher prevalence of obesity/morbid obesity than Hispanic and non-Hispanic white women. Prevalence of overweight is highest in Hispanic men and women aged ≥60 years, and non-Hispanic black women.

In the U.S. adult population, obesity levels remain high, irrespective of age, sex, and ethnicity. Overall, 73% of men and 65% of women were categorized as overweight, obese, or morbidly obese. There is a need for effective preventive interventions to reduce the burden of obesity.
1681-P

Inverse Associations between Circulating SFRPS and Adiposity among African-Caribbean Men

HIRA ALI, JOSEPH M. ZUMUDA, RYAN CVEJKUS, ERIN E. KERSHAW, ALLISON L. KUIPERS, CLAREANN H. BUNKER, IVA MILJKOVIC, PITTSBURGH, PA

Background: African ancestry populations are at the epicenter of the obesity and diabetes epidemic. Secreted frizzled-related protein 5 (SFRPS) is a negative adipokine and Wnt pathway modulator which is thought to be inversely related with adiposity and diabetes risk, however data in humans is conflicting. Therefore, we examined the association of SFRPS with parameters of obesity and insulin resistance among an African ancestry population.

Methods: We measured fasting serum SFRPS in a pilot study of 139 elderly Afro-Caribbean men (mean age 71.7 years, mean BMI 27.6 kg/m²). These men represented a random subset of a population-based study comprising ~3000 African ancestry men with anthropometrics, DXA measured adiposity, and fasting morning blood collections for biomarker analysis. SFRPS was measured in duplicate in previously unthawed serum with ELISA.

Results: Using Pearson correlations, we found SFRPS level to be positively associated with age (R = 0.18, p = 0.03) and negatively associated with BMI (R = -0.14, p = 0.09), waist circumference (R = -0.18, p = 0.02) and DXA trunk fat (R = -0.24, p = 0.003), independent of age. Among nonob diabetics (N=87), SFRPS was inversely associated with fasting insulin levels (R = -0.21, p = 0.04) and to some extent with HOMA-IR (R = -0.20, p = 0.06), independent of age and BMI. However, after adjustment for age and waist circumference, the associations between SFRPS and fasting serum insulin and HOMA-IR were no longer significant.

Conclusion: Our findings suggest that among African ancestry men, SFRPS may have a beneficial role against general and central obesity. Our findings also suggest that the link between SFRPS and diabetes risk in African Ancestry men may be explained by its correlation with central adiposity. Additional larger studies among African ancestry populations are needed to explore this novel biomarker along with its temporal relationship with clinically relevant metabolic outcomes.

Supported By: National Institutes of Health

1682-P

Prognostic Cut Points for Prediabetes Glucose Levels and HbA1c Values in Predicting All-Cause Mortality—A Systematic Review and Meta-analysis

MINXUAN HUANG, UNJALI J. GUJRAL, SIRAN HE, RAM JAGANNATH, JINGKAI WEI, LISA R. STAIMEZ, K.M. VENKAT NAHRAYAN, ATLANTA, GA, CHAPEL HILL, NC

Elevated but nondiabetic glucose levels, including impaired fasting glucose (IFG), 2-hour impaired glucose tolerance (IGT), and glycosylated hemoglobin (HbA1c), are associated with increased risk for all-cause mortality. However, the glucose measures may differ in their abilities to predict adverse outcomes. The World Health Organization (WHO) and the American Diabetes Association (ADA) also differ in their definitions of IFG, and it remains unclear which definition best predicts future adverse outcomes. The objective of this study was to evaluate the prognostic value of different cut-points of prediabetic glucose measures for predicting all-cause mortality in individuals without diabetes. In databases including MEDLINE, PubMed, Embase, Clinicaltrials.gov, WHO International Clinical Trials Registry Platform, and Cochrane, we screened prospective cohort studies with minimum 3 years of follow-up, in adults without diabetes at enrollment. Data from eligible studies were pooled to synthesize results for each glucose measure. Random effect regression model was used to calculate pooled hazard ratio or relative risk for all-cause mortality. We screened over 4,000 abstracts and identified 170 eligible studies with mean follow-up of 10.2 years. Compared with individuals with normal glycemia, those with IFG defined by the WHO criteria had 1.14 times increased risk for all-cause mortality. There was no significant increase in mortality risk among those with IFG diagnosed by the ADA criteria. Individuals with IGT had 1.17 times higher risk for all-cause mortality compared with individuals with normal glycemia. HbA1c as low as 5.5% was associated with an increased risk for all-cause mortality. The WHO criteria for IFG seems to have better predictive value for all-cause mortality than the ADA criteria. Furthermore, individuals with HbA1c levels at 5.5% may have higher risk for mortality.

Supported By: World Health Organization

Table. Estimated Number and Percentage of U.S. Adults Categorized as Overweight, Obese, or Morbidly Obese, Stratified by Age, Sex, and Ethnicity (Pooled Data Across Five Surveys from 2003-2012).

<table>
<thead>
<tr>
<th>BMI category</th>
<th>Men (n=307,2 M)</th>
<th>Women (n=216,6 M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (≥ 25 kg/m²)</td>
<td>73% (216.3 M)</td>
<td>65% (146.6 M)</td>
</tr>
<tr>
<td>Prevalence (%)</td>
<td>Prevalence (%)</td>
<td></td>
</tr>
</tbody>
</table>

Obese/morbidly obese (≥ 30 kg/m²)

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Men (n=107,2 M)</th>
<th>Women (n=116,6 M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hispanic white</td>
<td>74% (75.5 M)</td>
<td>63% (48.2 M)</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>70% (7.9 M)</td>
<td>82% (11.9 M)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>78% (12.3 M)</td>
<td>75% (12.1 M)</td>
</tr>
<tr>
<td>Prevalence (%)</td>
<td>Prevalence (%)</td>
<td></td>
</tr>
</tbody>
</table>

Age (years)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Men (n=137,2 M)</th>
<th>Women (n=136,6 M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-39</td>
<td>65% (26.0 M)</td>
<td>59% (23.7 M)</td>
</tr>
<tr>
<td>40-59</td>
<td>79% (22.9 M)</td>
<td>68% (29.4 M)</td>
</tr>
<tr>
<td>≥60</td>
<td>75% (19.5 M)</td>
<td>71% (22.3 M)</td>
</tr>
<tr>
<td>Prevalence (%)</td>
<td>Prevalence (%)</td>
<td></td>
</tr>
</tbody>
</table>

BMI category Men Women

| ≥40 kg/m² | 71% (11.4 M) | 71% (11.4 M) |

Obese/morbidly obese (≥ 40 kg/m²)

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Men (n=137,2 M)</th>
<th>Women (n=136,6 M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hispanic white</td>
<td>74% (75.5 M)</td>
<td>63% (48.2 M)</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>70% (7.9 M)</td>
<td>82% (11.9 M)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>78% (12.3 M)</td>
<td>75% (12.1 M)</td>
</tr>
<tr>
<td>Prevalence (%)</td>
<td>Prevalence (%)</td>
<td></td>
</tr>
</tbody>
</table>

Age (years)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Men (n=137,2 M)</th>
<th>Women (n=136,6 M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-39</td>
<td>30% (12.0 M)</td>
<td>33% (13.5 M)</td>
</tr>
<tr>
<td>40-59</td>
<td>36% (17.5 M)</td>
<td>36% (16.9 M)</td>
</tr>
<tr>
<td>≥60</td>
<td>36% (8.4 M)</td>
<td>36% (12.4 M)</td>
</tr>
<tr>
<td>Prevalence (%)</td>
<td>Prevalence (%)</td>
<td></td>
</tr>
</tbody>
</table>

Obese/morbidly obese (≥ 40 kg/m²)

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Men (n=137,2 M)</th>
<th>Women (n=136,6 M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hispanic white</td>
<td>5% (1.6 M)</td>
<td>6% (0.1 M)</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>6% (0.9 M)</td>
<td>7% (1.1 M)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>4% (0.9 M)</td>
<td>7% (1.1 M)</td>
</tr>
<tr>
<td>Prevalence (%)</td>
<td>Prevalence (%)</td>
<td></td>
</tr>
</tbody>
</table>

Age (years)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Men (n=137,2 M)</th>
<th>Women (n=136,6 M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-39</td>
<td>5% (2.0 M)</td>
<td>8% (3.3 M)</td>
</tr>
<tr>
<td>40-59</td>
<td>5% (2.1 M)</td>
<td>10% (4.3 M)</td>
</tr>
<tr>
<td>≥60</td>
<td>5% (1.3 M)</td>
<td>7% (2.3 M)</td>
</tr>
<tr>
<td>Prevalence (%)</td>
<td>Prevalence (%)</td>
<td></td>
</tr>
</tbody>
</table>

Obese/morbidly obese (≥ 50 kg/m²)

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Men (n=137,2 M)</th>
<th>Women (n=136,6 M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hispanic white</td>
<td>5% (1.6 M)</td>
<td>6% (0.1 M)</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>6% (0.9 M)</td>
<td>7% (1.1 M)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>4% (0.9 M)</td>
<td>7% (1.1 M)</td>
</tr>
<tr>
<td>Prevalence (%)</td>
<td>Prevalence (%)</td>
<td></td>
</tr>
</tbody>
</table>

Obese/morbidly obese (≥ 60 kg/m²)

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Men (n=137,2 M)</th>
<th>Women (n=136,6 M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hispanic white</td>
<td>5% (1.6 M)</td>
<td>6% (0.1 M)</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>6% (0.9 M)</td>
<td>7% (1.1 M)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>4% (0.9 M)</td>
<td>7% (1.1 M)</td>
</tr>
<tr>
<td>Prevalence (%)</td>
<td>Prevalence (%)</td>
<td></td>
</tr>
</tbody>
</table>
Epidemiology/POSTERS

1683-P

Serum Levels of Soluble LR11 Are Associated with Insulin Resistance in the Patients with Type 2 Diabetes Mellitus
HIROYUKI UNOKI-KUBOTA, MEIZI JIANG, HIROSHI KAJIO, RITSUKO YAMADA-MOTO-HUNDA, KAZUYUKI TOBE, MITSUHIKO NODA, HIDEAKI BLUO, YASHI SHUKURI, KABURAGI, Tokyo, Japan, Satoka, Japan, Toyama, Japan, Saitama, Japan

Obesity is now a worldwide epidemic, with overweight, obesity, and morbidity obesity all increasing. Recently, there is increasing support that obesity is a major risk factor for developing insulin resistance and type 2 diabetes mellitus (T2D). Plasma soluble low-density lipoprotein receptor-relative with 11 ligand-binding repeats (sLR11) plays a role in the development of atherosclerosis, and has also been linked to the metabolism of triglyceride-rich lipoproteins and adiposity. To assess the relationship between sLR11 levels and T2D, we analyzed the sLR11 levels in T2D patients. Serum sLR11 levels were measured in 70 patients with T2D (mean age 60.8 ± 7.0, 68.8% males, and BMI 24.7 ± 3.2) and 76 healthy control subjects (mean age 58.5 ± 6.5, 65.8% males, and BMI 24.1 ± 2.5) by ELISA. Circulating sLR11 levels were significantly increased in T2D patients compared with healthy control subjects (10.2 ± 4.2 vs. 8.3 ± 2.1, P = 1.4 × 10^-15). Stepwise multivariate regression analysis showed that serum sLR11 levels were significantly associated with HOMA-IR (β = 0.26, P = 4.8 × 10^-4), BMI (β = 0.24, P = 1.0 × 10^-4) and age (β = 0.20, P = 2.7 × 10^-4). Logistic regression analyses indicated that sLR11 was independently associated with HOMA-IR (odds ratio [OR], sLR11 tertile increment: 8.61, 95% confidence interval [CI]: 1.71—27.13) and BMI (OR, sLR11 tertile increment: 1.86, 95% CI: 1.03—3.35). We then analyzed a gene dosage effect that links LR11 expression to insulin resistance and obesity using db/db mice with genetic loss of LR11 (LR11-KO db/db). LR11-KO db/db mice displayed significantly lower fasting plasma glucose and insulin levels, and improved glucose tolerance compared with age-matched db/db mice, although there was no significant difference in body weight between them. Our findings imply that LR11 may be mechanistically involved in the prevalence and development of insulin resistance and T2D.

Supported By: Japan Society for the Promotion of Science

1684-P

Association between Polycystic Ovarian Syndrome and Bone Mineral Density—A Systematic Review and Meta-analysis
SIKARIN UFAL, DAVID A. EHRENNANN, Chicago, IL

Background: Polycystic ovarian syndrome (PCOS) affects at least 17-20% of female population. Little information is available about whether PCOS is related to low bone mineral density (BMD). In this meta-analysis, we try to explore and compare PCOS patient and normal female population to determine the relation between PCOS patients and osteoporosis as an outcome.

Methods: Two investigators searched published studies indexed in MEDLINE and EMBASE. This review included published observational studies evaluating the association between PCOS and bone mass, BMD, or osteoporosis. PCOS is diagnosed based on clinical, biochemical, radiological findings per Rotterdam criteria. The primary outcome of this study were differences in the total BMD (g/cm²) or BMD at different anatomical sites including lumbar spine, pelvis, femoral and total body as measured by dual-energy X-ray absorptiometry between patients with PCOS and participants without PCOS (controls).

Results: Five cross sectional studies involving 1276 participants were included. Meta-analysis using the random-effects model to examine the difference in outcomes between PCOS and controls are performed. The pooled mean difference of total BMD in patients who have PCOS vs. controls in the five studies was -0.22 (95% confidence interval, -0.66 to 0.23; P = 0.39). The statistical between-study heterogeneity may represent substantial heterogeneity with an I² of 99% (p<0.01). For femoral neck BMD, the difference was not statistically significant, which was 0.00 (95% confidence interval, -0.03 to 0.02; P = 0.81). For lumbar spine BMD, the difference was also not statistically significant, which was -0.02 (95% confidence interval, -0.06 to 0.02; P = 0.25).

Conclusion: Women with PCOS have seemed to increase a chance of having osteoporosis more than the normal population. The real mechanism of PCOS and osteoporosis and a larger PCOS population need to be clarified and study more in the future.

1685-P

Trends in Glycemic Control Based on A1C Factorisation across Different Clinical Settings
PURVI M. CHAWLA, CHANDRASHEKHAR ASHTEKAR, RAHUL M. DHOPE, AMBARI FIRDUS, SHAIKH, MIKHIL C. KOTHARI, MANOJ S. CHAWLA, Mumbai, India, Pune, India

Approximately, 20-40% patients with diabetes achieve the glycemic target (A1C<7%), globally. A retrospective analysis of glycemic trends based on A1C across three diabetes specialties centers (metro city (A), second tier city (B), district headquarter (C)) including 11,162 patients (A =n=3601, B =n=156, C =n=7648) either newly diagnosed or following up at over past two years, was undertaken. Being treated as per standard guidelines with at least one HbA1c level reported within this period and classified as well-controlled (A1C<7%) or uncontrolled (A1C>7%) based on glycemic factorization. Table 1 shows the ANOVA results(1264 patients (11.32%) achieving an A1C<6%, and 2708 patients (24.27%) between 6-6.9% across centers); representing well-controlled patients and the uncontrolled patient population (A1C>7%). The latter group with 22.52% (n=2514) and 23.49% (n=2622) patients with A1C between 7-7.9% and 8-9.9% respectively, represented a group that should be aggressively treated to mitigate the “missed opportunities” in achieving glycemic control and increase the overall percentage of patients achieving target goals. Furthermore, sub-group analyses across individual centers (A, B, C) revealed that differences in factorized HbA1c levels were statistically highly significant (p<0.002) necessitating a high-quality, uniform standard of care, irrespective of the setting to help curb of this disease.

<table>
<thead>
<tr>
<th>A1C Factorisation</th>
<th>Metro City (A)</th>
<th>Second Tier City (B)</th>
<th>District Headquarter (C)</th>
<th>Total</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6</td>
<td>261</td>
<td>52</td>
<td>951</td>
<td>1264</td>
<td>11.32</td>
</tr>
<tr>
<td>6-6.9</td>
<td>999</td>
<td>187</td>
<td>1523</td>
<td>2709</td>
<td>24.27</td>
</tr>
<tr>
<td>7-7.9</td>
<td>1037</td>
<td>191</td>
<td>1286</td>
<td>2514</td>
<td>22.52</td>
</tr>
<tr>
<td>8-9.9</td>
<td>911</td>
<td>224</td>
<td>1487</td>
<td>2622</td>
<td>23.49</td>
</tr>
<tr>
<td>10-10.9</td>
<td>183</td>
<td>72</td>
<td>482</td>
<td>737</td>
<td>6.6</td>
</tr>
<tr>
<td>≥11.1-11.9</td>
<td>116</td>
<td>30</td>
<td>361</td>
<td>507</td>
<td>4.54</td>
</tr>
<tr>
<td>&gt;12</td>
<td>94</td>
<td>59</td>
<td>656</td>
<td>809</td>
<td>7.25</td>
</tr>
</tbody>
</table>

Total: 3601 815 6746 11162

Epidemiology—Type 1 Diabetes

1686-P

Moderated Poster Discussion: Type 1 Diabetes Autoimmunity (Posters: 1686-P to 1691-P, see page 22)

Residual Beta-Cell Function in Long Duration Type 1 Diabetes (T1D)
ROSE DUBITOSKI-KLUG, BARBARA BRAFFET, SUSAN M. HITT, VALERIE ARENDSD, MICHAEL STEFFES, AMY K. SAENGER, JOHN LACHIN, JERRY P. PALMER, Cleveland, OH, Rockville, MD, Columbia, MO, Minneapolis, MN, Seattle, WA

We investigated residual beta cell function in participants from the DCCT/EDIC study with an average of 35 (range 27, 48) years duration of T1D. Between 2015-2017 after 22-24 years of follow-up in EDIC, a 4-hour mixed meal tolerance test was administered to 944 participants and 7 timed plasma specimens were collected and assayed for C-peptide using a chemiluminescent immunoassay (Roche). We defined a significant post-stimulus response as a peak C-peptide concentration >0.03 nmol/L, based on an earlier DCCT study which demonstrated that the risk of microvascular disease progression was markedly higher among participants who entered the trial with values below this concentration. Overall, 71 (7.5%) participants were classified as “responders” with a median peak C-peptide of 0.10 nmol/L (IQR 0.06, 0.15). Among the 873 participants classified as “non-responders,” 46 had detectable peak C-peptide between 0.003 (limit of detection) and 0.029 nmol/L. Responders were slightly older than non-responders (58.5 ± 6.2 vs. 56.5 ± 6.8 years, p=0.02), yet had similar age of onset of diabetes (22.5 ± 7.0 vs. 21.4 ± 7.8 years) and duration of diabetes (35.9 ± 5.1 vs. 35.0 ± 4.9 years). Compared to non-responders, responders had lower HbA1c values (8.6 ± 1.7 vs. 8.9 ± 1.5%, p=0.01) and higher stimulated C-peptide (0.22 ± 0.14 vs. 0.11 ± 0.11 nmol/L, p<0.001) at DCCT baseline; and had lower insulin requirements both at DCCT baseline (0.54 ± 0.18 vs. 0.67 ± 0.24 units/kg/day, p<0.001) and throughout DCCT follow-up (0.61 ± 0.20 vs. 0.69 ± 0.19 units/kg/day).

Moderated Poster Discussion  ADA-Supported Research
Significantly fewer responders experienced severe hypoglycemia (requiring assistance) throughout the DCC/EDIC study (45% of responders vs. 70% of non-responders; p<0.0001). Both the initial episode and recurrences of severe hypoglycemia were less frequent with increasing C-peptide concentrations.

In conclusion, beta cell function persists in some very long duration T1D patients and is associated with clinically meaningful reductions in the frequency of severe hypoglycemia. Supported By: National Institute of Diabetes and Digestive and Kidney Diseases

**1687-P**

**Risk of Islet and Celiac Autoimmunity in Cotwins of Probands with Type 1 Diabetes**

TAYLOR M. TRIOLE, ALEXANDRA R. FOUTS, LAURA PYLE, LIPEING YU, PETER GOTTLIEB, ANDREA STECK, Aurora, CO

Concordance for persistent islet autoimmunity (IA) and type 1 diabetes (T1D) in monozygotic twins (MZ) after one twin is diagnosed has been highly variable (30-70%), while risk for development of IA in dizygotic twins (DZ) is thought to be similar to non-twin siblings. Since 1995, the Twin Family Study at the Barbara Davis Center has followed 336 twins (168 twin probands diagnosed with T1D and 168 cotwins) with a median follow-up of 14 years (IQR:10-18 years). Zygosity testing confirmed a total of 80 MZ pairs and 88 DZ pairs. Cotwins were followed for the development of IA and celiac autoimmunity (CDA). In MZ cotwins, cumulative incidence for IA was 14% by age 20 and 63% by age 45, while development of CDA was 10% by 20 years. Development of IA and CDA by age 20 was 9.2% and 12.3% in DZ cotwins respectively, with development of IA reaching 70% by age 30 (Figure). In Cox proportional hazards models, only the proband’s age at diagnosis, but not sex, HLA-DR3 nor DR4 were associated with time to IA and CDA in cotwins. In MZ twins, younger age of the proband was associated with an increased hazard ratio (HR) for both IA and CDA, while younger age in DZ twins was associated with an increased HR for IA only.

In conclusion, CDA risk does not appear to increase after age 15. With long term follow-up, cumulative incidence for IA is high in DZ twins, similar to MZ twins, suggesting a role of possible early environmental factors shared by T1D-discordant cotwins. Supported By: American Diabetes Association (1-14-CD-17 to A.S.); National Institute of Diabetes and Digestive and Kidney Diseases (5T32DK063687-14 to T.M.T.)

**1688-P**

**Time-to-Peak C-Peptide and Peak Glucose during an Oral Glucose Tolerance Test (OGTT) Are Independent Risk Factors for Type 1 Diabetes (T1D) in Antibody-Positive (Ab+) Individuals**

HEBA M. ISMAIL, PING XU, CARMELLA EVANS-MOLINA, JERRY P. PALMER, JAY GOTTLIEB, ANDREA STECK, Pittsburgh, PA; Tampa, FL; Indianapolis, IN; Seattle, WA; Miami, FL

Peak C-peptide (C-P) and glucose levels are known predictors of T1D, but T1D prediction by times to peak C-P or glucose during OGTTs in 709 T1D prediction by times to those peak levels has not been studied. We thus assessed T1D prediction by times to peak C-P or glucose during OGTTs in 709 Ab+ Diabetes Prevention Trial-type participants with 2-hour OGTTs (mean age: 13.9±1.8 years; BMI percentile [%ile]: 59.3±20.0; 56% male). Log rank testing and Cox regression with adjustments for age, sex, BMI %ile, proband relation, HLA, and Ab number were used. Risks were higher for time to peak C-P >60 mins [HR: 1.96 (CI: 1.49-2.63), p<0.001] and for time to peak glucose >30 mins [HR: 2.22 (1.67-2.94), p<0.001]. With time to peak C-P and peak C-P as covariates, T1D associations were greater for time to peak C-P (X2=22.8 vs. 9.3, both p<0.001). Time to peak glucose and peak glucose associations also remained significant (both p<0.001). Findings were validated in Ab+ relatives in the TrialNet Pathway to Prevention study (Figure); those with a peak C-P >60 mins or a peak glucose >30 mins had higher risk (both p<0.001).

In conclusion, Ab+ relatives with delayed peak C-P or glucose are at higher T1D risk, independent of peak levels. Moreover, the time to peak C-P appears to be more predictive than the peak level. Times to peak C-P and glucose have potential use as predictors of T1D and as markers for progression.

**Related Abstract**

**451**

**Continuous Glucose Monitoring Predicts Progression to Diabetes in Autoantibody-Positive Children**

ANDREA STECK, FRAN DUNN, IMAN TAKI, MICHELLE R. HOFFMAN, KIMBER SIMMOND, BRIGITTE F. FRÖHNET, MARIAN REVERS, Aurora, CO; Denver, CO; Highlands Ranch, CO

Children with islet autoantibodies (Ab+) are at high risk for developing clinical type 1 diabetes (T1D) and need accurate surveillance for prediction and diagnosis of T1D. Monitoring typically utilizes repeated 2-hour oral glucose tolerance tests. The objective of this study was to explore whether continuous glucose monitoring (CGM) could be an alternative measure for T1D prediction. In the Diabetes Autoimmunity Study in the Young (DAISY), 23 Ab+ subjects with a baseline CGM were followed for development of T1D for a mean of 28 months (8 of these progressed to T1D at a mean age of 15.2 years). Compared to non-progressors, subjects who progressed to T1D had significantly increased glycemic variability (SD 29 vs. 21 mg/dL, p=0.047). Supported By: The Leona M. and Harry B. Helmsley Charitable Trust
daytime sensor average (122 vs. 106 mg/dl, p=0.02), and daytime sensor AUC (p=0.047). They spent 24% of time above 140 mg/dl and 12% above 180 mg/dl compared to, respectively, 8% and 3% (both p=0.005) for non-progressors; time spent over 200 mg/dl was minimal and not different between groups. Performance of prediction by receiver operating curve (ROC) analyses showed AUC of 0.85 for both 36me in terms of having ≥240 mg/dl and 180 mg/dl. The cutoff of 18% time spent above 140 mg/dl had 100% specificity and 100% PPV with good sensitivity for diabetes prediction (Table).

In conclusion, ≥18% CGM time spent above 140 mg/dl accurately predicts progression to clinical diabetes in islet Ab+ children.

Table.

<table>
<thead>
<tr>
<th>Index</th>
<th>Cutoff</th>
<th>PPV</th>
<th>NPV</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤120</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥121</td>
<td>36%</td>
<td>0.71</td>
<td>0.81</td>
<td>0.625</td>
</tr>
<tr>
<td>≥140</td>
<td>18%</td>
<td>1.00</td>
<td>0.88</td>
<td>0.750</td>
</tr>
<tr>
<td>≥160</td>
<td>6%</td>
<td>0.63</td>
<td>0.82</td>
<td>0.625</td>
</tr>
<tr>
<td>≥180</td>
<td>2%</td>
<td>0.71</td>
<td>0.81</td>
<td>0.625</td>
</tr>
<tr>
<td>≥200</td>
<td>0.2%</td>
<td>0.54</td>
<td>0.86</td>
<td>0.750</td>
</tr>
</tbody>
</table>

Supported By: American Diabetes Association (1-4-CD-17 to A2; National Institutes of Health)

1691-P

Individuals with Single Islet Autoantibody Positivity (SA+) at Type 1 Diabetes (T1D) Diagnosis Have Distinct Characteristics

MARIA J. REDONDO, JAY SOSENKO, INGRID LIBMAN, JENNIFER J. MCVEA, MARK A. ATKINSON, DOROTHY J. BECKER, SUSAN GEYER, THE TYPE 1 DIABETES TRIALNET STUDY GROUP; Houston, TX; Miami, FL; Pittsburgh, PA; Minneapolis, MN; Gainesville, FL; Tampa, FL.

Multiple autoantibody positivity (MA+) usually precedes clinical T1D. However, a subset of patients who develop T1D have SA+. We hypothesized that individuals who at T1D diagnosis express SA+ compared with MA+ have different demographic, metabolic, immunologic, and genetic characteristics. We studied 620 TrialNet participants who developed clinical T1D (median age=12.3 years range=14.58, 47.5%, male, 38%, white). Using multivariable modeling and adjusting for potential confounders, we investigated differences between participants with SA+ vs. MA+ of autoantibodies to GADA65 (GADA), insulin (mIAA), IA2, ZnT8 and ICA at T1D diagnosis. We found 95 participants who had SA+ [70% GADA+] and 525 participants with MA+. In univariate analyses, individuals with SA+ vs. MA+ were older at T1D diagnosis (median 16.4 vs. 11.7 years, p<0.001) and had higher fasting C-peptide (1.87 ± 1.47 nmol/L, p=0.007), higher 30-minute C-peptide difference (1.42 ± 1.18, p=0.009) and lower Index60 (composite measure of fasting C-peptide, 60-min glucose and 60-min C-peptide (2.31 vs. 2.9, p=0.005)). Gender, race, ethnicity, BMI-Z-score, presence of HLA DR3-DQ2 and/or DR4-DQ8, fasting glucose, AUC glucose and AUC C-peptide were not significantly different. By multivariable analyses, SA+ at onset corresponded with older age (OR=1.05, p=0.001), lower Index60 (OR=0.77, p=0.008), and lower likelihood of mIAGA (OR=0.27, p<0.001) and GADA+ (OR=0.25, p<0.001); gender, HLA, BMI-Z-score and other autoantibody types were not significantly different. Independent factors of being SA+ differed between DR3/DR4/DQ8 heterozygous participants (older age and not having mIAA+ or GADA+)(p<0.01) and those not DR3/DR4/DQ8 (lower Index60 and not having GADA+)(p<0.01).

In conclusion, the number of islet autoantibodies at T1D diagnosis is associated with distinct characteristics, which may suggest heterogeneous pathogenesis with relevance for T1D prevention and treatment.

Supported By: National Institutes of Health (U01DK08610, U01DK065034, U01DK061042, U01DK061058, U01DK085465, U01DK063463, U01DK085461, U01DK085466, U01DK085459, U01DK085504, U01DK085509, U01DK082180, U01DK083513, U01DK085476, U01DK082180, U01DK08228, U01DK085684, U01DK070213, U01DK070174, U04DK078890)

1692-P

A Comparison of HbA1c and Index 60 Thresholds for Identifying Autoantibody Positive Individuals at High Risk for Type 1 Diabetes (T1D)

LAURA M. JACOBSEN,HEBA M. ISMAIL, MARK A. CLEMENTS, DESMOND SCHATZ, JAY SOSENKO, Gainesville, FL; Pittsburgh, PA; Kansas City, MO; Miami, FL.

Current ADA standards include HbA1c values 5.7%–6.4% as an indicator of prediabetes. However, there is little information with regard to HbA1c as a specific predictor of T1D. We thus compared HbA1c with Index 60, a T1D marker, for identifying individuals at high risk for T1D. Index 60 was derived from a proportional hazards regression model for T1D that included log fasting C-peptide, 60-minute glucose, and 60-minute C-peptide. Diabetes Prevention Trial-type 1 participants with Index 60 ≥2.00 at baseline were followed for the first (incident) OGTT exceeding an Index 60 ≥2.00 threshold (n=84). Similarly, those with HbA1c values ≥6.0% at baseline were followed for the first (incident) HbA1c ≥6.0% (n=77). Those with both incident Index 60 ≥2.00 and incident HbA1c ≥6.0 were excluded. At the incident OGTTs, those with HbA1c ≥6.0 were older (19.2±12.2 years vs. 12.7±7.2 years, p<0.001). The cumulative incidence for T1D was higher (log rank p<0.001) after Index 60 ≥2.00 than after HbA1c ≥6.0 (3- and 4-year risks for HbA1c ≥6.0: 0.41 and 0.45; 29/77 diagnosed vs. 3- and 4-year risks for Index 60 ≥2.00: 0.78 and 0.92, 90/85 diagnosed). The hazard ratio for Index 60 ≥2.00 vs. HbA1c ≥6.0 (with age adjustment) was significant (HR: 1.96 (1.20, 3.16), p=0.006). Intervals from incident Index 60 ≥2.00 and HbA1c ≥6.0 to diagnosis were 1.2±0.9 (0.1-3.8 years) and 1.0±1.0 (0.4-7.7 years, respectively (p=0.50). The 59 individuals who had OGTTs on the date of incident HbA1c ≥6.0 had higher 30-minute C-peptide (with age adjustment) than those with incident Index 60 ≥2.00 (2.8±1.9 ng/ml vs. 1.6±1.0 mg/ml, p<0.001).

In conclusion, Index 60 ≥2.00 was superior to HbA1c ≥6.0 at identifying individuals at high risk for T1D. Moreover, those with incident HbA1c ≥6.0 were much older with higher C-peptide levels, suggesting heterogeneity. These findings add support for including C-peptide together with glucose in developing predictors and pre-diagnostic endpoints that are specific for T1D.
Supporting Information

**Table. Three Year Outcomes with Omnipod System Use.**

<table>
<thead>
<tr>
<th>Variable (mean)</th>
<th>Total Cohort</th>
<th>Patients with 3 year follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-Omipod</td>
<td>Post-Omipod</td>
</tr>
<tr>
<td>Age, yr</td>
<td>1 yr (n=207)</td>
<td>1 yr (n=135)</td>
</tr>
<tr>
<td></td>
<td>13.9±17.0</td>
<td>14.4±14.6</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.0±5.5</td>
<td>27.3±5.4</td>
</tr>
<tr>
<td>Insulin dose, U/kg/d</td>
<td>0.82±0.76</td>
<td>0.76±0.82</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>7.6±8.9</td>
<td>7.8±7.4</td>
</tr>
<tr>
<td>Severe hypoglycemia (level 3 patients affected per year, %)</td>
<td>5.2±5.5</td>
<td>4.3±3.7</td>
</tr>
<tr>
<td>Severe hypoglycemia (total patients affected per year, %)</td>
<td>1.5±1.4</td>
<td>1.4±0.5</td>
</tr>
<tr>
<td>DKA patients affected per year, %</td>
<td>5.8±3.8</td>
<td>3.0±2.1</td>
</tr>
</tbody>
</table>

**1695-P**
Reduced Rate of Acute Complications with Tubless Insulin Pump Use—Data from 2,640 Patients in the German/Austrian DPV Registry
TORBEN BIESTER, THOMAS DANNE, ESTHER BOLLOW, ANKE SCHWANDT, BETTY SCHULZ, THOMAS WERDER, MELLENDE BÖTTGER, CECILIA KÖPLER, CHRISTOPH VOOGT, M. KLOP, ALEXANDER KESSLER, MARCEL KEMPEN, ANDREAS PRÉSE, KARL-HEINZ EHRMANN, GERHARD LILL, LUDWIG HAUPT, JAKOB RÖTMANN, SABINE POHL.

Little is known about the rates of acute complications when switching from MDI or traditional insulin pumps to tubless insulin pump therapy. The German/Austrian Diabetes patients follow-up-registry (DPV) includes 2,691 German/Austrian Diabetes patients followed up (n=1,769, 65.4%) and 1,011 patients (n=956, 34.6%) using a tubless insulin pump (Omnipod® Insulin Management System, Insulet Corp, Billerica, MA) since 2012. Patients with type 1 diabetes had a mean age of 12.3 years (IQR 9.6-15.0), diabetes duration 2.5 year [0.7-5.9], HbA1c 7.7% [6.8-8.3]. The prior treatment modality was 59.3% MDI, 37.5% other pump and 2.4% tubeless pump (Omnipod®). Despite smaller proportions of DKA, insulin requirements increased with eGDR categories: C1 2.6%; C2 6.4% (HR 2.32, 95% CI 0.93-5.77); C3 11.4% (0.78-3.95); C4 21.1% (8.07, 3.74-17.40, p<0.001). Only adjustment for variables strictly related to IR (HDL, TG, albuminuria) remained significantly associated with CVD among adults with type 1 diabetes.

**1696-P**
Overweight Individuals with Type 1 Diabetes Are Less Likely to Present with Diabetic Ketoadiposis—Data from the After Diabetes Diagnosis Research Support System (ADDRESS-2) Cohort
SHIVANI MISRA, AKAA KAUR, IAN F. GODFLAND, HELEN C. WALKLEY, DESMOND G. JOHNSTON ESQ., NICK OLIVER.

Introduction: Insulin resistance has been proposed to accelerate progression to type 1 diabetes (T1D) in antibody positive relatives of affected individuals. We hypothesised that overweight individuals with confirmed T1D would be less likely to present with diabetic ketoacidosis (DKA), signifying an earlier onset of T1D, due to concomitant insulin resistance.

Methods: The ADDRESS-2 study recruits incident clinician-assigned T1D cases within 6-months of diagnosis and systematically assesses pancreatic autoimmunity by GAD-65, IA-2 and ZnT8 antibodies. People with at least two positive antibodies were selected to confirm diagnosis of T1D and categorised for adiposity according to BMI (adults) or Z-scores (children). Odds ratios (OR) for presentation with DKA were compared, adjusted for potential confounders and sub-analysed by whether adult or child at recruitment.

Results: 31% (969/3122) were positive for two or more pancreatic antibodies. Of these 44% (424/969) presented with DKA. The proportions with DKA varied significantly by adiposity: 59% underwaterweight (16/27), 47% normal weight (280/601), 39% overweight (103/263), 30% obese (15/63) and 40% severely obese (26/61) (p=0.02). When adjusted for age, being overweight or obese was associated with lower risk of DKA in adults (OR 0.58, p=0.006; 0.44, p=0.03, respectively) not children (OR 0.9, p=0.81; 0.51, p=0.12, respectively).

Conclusions: Adult T1D are less likely to present with DKA if overweight or obese. Despite smaller proportions of DKA, insulin requirements are higher. These data suggest that, in adults, T1D presentation is masked by insulin resistance.
Epidemiology/Genetics

1698-P
Teraspanin 7 Autoantibodies in Type 1 Diabetes and Latent Autoimmune Diabetes in Adult
ZHIGUANG ZHOU, XIAJIE SHI, PEILIN ZHENG, GAN HUANG, YANFEI WANG, CHAO DENG, CHANGTAI CHINA

Objective: This study aimed to investigate the prevalence of the newly-identified islet autoantibody, tetraspanin 7 autoantibody (TSPAN7A) in Chinese type 1 diabetes (T1D) and latent autoimmune diabetes in adults (LADA), and the correlation between TSPAN7A and islet function in LADA patients.

Research Design and Methods: Patients with newly onset T1D (n=158), long-lasting T1D (n=157), LADA (n=170), type 2 diabetes (T2D; n=204) and healthy control subjects (n=170) were recruited for the cross sectional study. Another cohort including 46 LADA patients with 3-year follow-up was recruited for the longitudinal study. TSPAN7A was assayed by luciferase immunoprecipitation system assay.

Results: The prevalence of TSPAN7A in newly onset T1D, non-newly onset T1D, T2D, and LADA and healthy control subjects were 25.3% (40/158), 10.2% (16/157), 0.5% (1/204), 21.1% (37/175) and 1.2% (2/170), respectively. Out of the 23 patients with newly onset T1D but negative for GADA, IA2 and ZnT8A, 3 patients were positive for TSPAN7A (13.0%) improving the detection of autoantibodies from 81.6% to 83.0% in T1D. In LADA patients, analysis of logistic regression demonstrated that duration (OR=1.77, P=0.026), GADA titer (OR=2.79, P=0.006) and TSPAN7A (OR=2.86, P=0.034) were the risk factors to islet function while BMI was the protection factor (OR=0.35, P=0.001). In the follow-up study, LADA patients with TSPAN7A showed a worse islet function compared those negative for TSPAN7A after 3-year diagnosis.

Conclusion: TSPAN7A is a novel diagnostic tool for T1D and LADA. Combination of TSPAN7A with other autoantibodies can improve the diagnosis of T1D. TSPAN7A is negatively correlated with islet function in LADA.

1699-P
Hidden Epidemic—Half of T1DM Is Diagnosed in Adulthood
MAAMOUN SALAM, YICHENG BAO, CYNTHIA J. HERRICK, JANET B. MCGILL, JING HUGHES, ST. LOUIS, MO Kansas City, MO

Objective: To determine the distribution of age of onset of T1D in an adult cohort of patients with T1DM.

Methods: T1DM patients from an adult academic diabetes center provided informed consent, completed a questionnaire and gave permission for blood collection. 1,167 confirmed cases of T1DM were included. Gender and age of onset of T1DM was defined as positive and negative, respectively. Postprandial C-peptide index was significantly lower in positive than negative patients with T2D (0.39±0.48 vs. 1.5±1.16, p<0.001), but not with AT1D. HLA was assessed in 15 patients with SPIDDM, nine positive and six negative for GADA. Seven of the nine positive, but none of the five negative, patients had HLA-DQ3 (p=0.007). HLA was also assessed in 39 patients with AT1D, 33 positive and six negative for GADA. Eleven of the 33 positive, but none of the six negative, patients had HLA-DR9 (p=0.158).

Discussion: In SPIDDM patients weakly positive for GADA by RIA, ELISA positivity was significantly associated with lower insulin secretion, suggesting that more cytotoxic epitopes of GAD are recognized by ELISA than by RIA. ELISA positivity in SPIDDM is associated with HLA-DR9, a haplotype linked to cytoktoxicity against pancreatic β-cells. Measuring GADA by RIA and ELISA may predict insulin secretion in patients with SPIDDM.

1701-P
Sclerostin Resistance Protects Bone Mass and Retards the Onset of Metabolic Abnormalities in a Mouse Model of Type 1 Diabetes
GUILIA LEANZA, ROCKY STRESILIO, PATRIZIA PIZZOTTI, ROBERTO CIVITELLI, NICOLA NAPOLI, ROME, Italy, St. Louis, MO

Type 1 diabetes (T1D) is characterized by bone fragility and increased risk of fracture. In humans and preclinical models of T1D, serum markers of bone formation are decreased suggesting reduced bone turnover rates. In a preliminary study, we found high circulating levels of the Wnt inhibitor sclerostin (Scl) in T1D patients. To test the potential role of Scl and Wnt in T1D bone disease, we introduced the Scl-resistant Lrpg31/+ mutation, associated with high bone mass (HBM), in mice carrying the Ins2Akita mutation (Akita), which causes hypoinsulinemia and hyperglycemia at age 4-5 week. Both Akita and Akita/HBM mice had developed hyperglycemia, compared to 80% of Akita mice (n=10), and at 8 weeks only 40% of Akita/HBM were hyperglycemic vs. 90% in HBM mice. At 6 and 8 weeks, only 30% of Akita/HBM mice had developed hyperglycemia, compared to 80% of Akita mice (n=10); and at 8 weeks only 40% of Akita/HBM were hyperglycemic vs. 90% in the Akita group. Only at 12 weeks was the majority of Akita/HBM mice hyperglycemic, as the Akita group. Furthermore, Akita mice exhibited a significant impairment in glucose tolerance in an intraperitoneal glucose tolerance test relative to Akita/HBM mice at 6 and 8 weeks (p=0.05 for differences in areas under the curve; n=6-8). Thus, Wnt signaling hyperactivation in Scl resistant mice may slow the onset of T1D, although it does not prevent it. No significant differences in weight and nose-tail length were found in Akita/HBM mutants and controls. Importantly, bone mass was 18% higher in Akita/HBM relative to Akita littermates at 12 weeks (p=0.001; n=6-8), a difference that persisted up until at least 18 weeks of age, despite prolonged hyperglycemia. Bone mass in compound mutants was not different relative to HBM mice. Thus, the metabolic changes caused by T1D do not alter the consequence of Scl resistance and Wnt hyperactivation on bone.

In summary, even though we have not yet measured bone strength, Wnt stimulation protects bone mass and may retard the onset of metabolic abnormalities in T1D.
Diving into Type 2 Diabetes Genetics (Posters: 1703-P to 1708-P), see page 20.

**1703-P**

The First Genome-Wide Association Study (GWAS) for Type 2 Diabetes in Youth from the Progress in Diabetes Genetics in Youth (ProDiGy) Collaboration

SHYLAJAI SRINIVASAN, JENNIFER TODD, LING CHEN, JASMIN DIVERS, SAM GUIDING, STEVEN CHERNALAUS, ROSE SUBITOZI-KLUG, MEGAN M. KELLY, KATHLEEN RACHANA SHAH, MAYRELLA HELEN BLACK, LYNNE E. WAGENKNECHT, JOSE M. MERCADER, ALISA MANNING, JASON FLANNICK, DANA DABLELA, JOSE C. FLOREZ, SAN FRANCISCO, CA, BOSTON, MA, WINSTON-SALEM, NC, WILMINGTON, DE, OKLAHOMA CITY, OK, CLEVELAND, OH, AURORA, CO, PHILADELPHIA, PA, ALISO VIEJO, CA, CAMBRIDGE, MA

The prevalence of type 2 diabetes is increasing in youth, particularly in certain ethnic groups, and studies have highlighted differences between youth- and adult-onset disease. However, its genetic determinants remain largely unexplored.

To identify genetic variants predisposing to type 2 diabetes in youth, we formed ProDiGy, a multi-ethnic collaboration of the TODAY, SEARCH for Diabetes in Youth, and T2D-GENES studies, with 3006 young cases (mean age=15.1 years ±2.8, 63% female, 22% white, 36% African American, 42% Hispanic) and 6061 diabetes-free adult controls (mean age = 54.2 years ±12.4, 57% female, 24% white, 18% African American, 58% Hispanic). After stratifying by self-reported and principal component-clustered ethnicity, we performed association analyses on 206,928 directly genotyped variants using a generalized linear mixed model using a genetic relationship matrix to account for population structure. We identified 5 genome-wide significant loci, including the novel locus rs13130484 in GNPDA2 (P = 1.4 ×10⁻⁹, odds ratio [OR]=1.24), which has nominal association with type 2 diabetes in adults. Known loci identified in our analysis include rs4132670 in the well-known type 2 diabetes locus TCFT212 (P = 2.6 ×10⁻⁸, OR=2.0), and rs7903146 [H1, a model rel-...](1454 characters)
Type 2 diabetes (T2D) is caused by interactions between genetic predisposition and environmental exposure. DNA methylation, a key epigenetic mark, integrates genetic variation and islet gene expression have identified expression quantitative trait loci (eQTL) that nominate target effector transcripts that variation in glycemia influences peripheral blood DNA methylation.

Supported By: National Institute of Diabetes and Digestive and Kidney Diseases (1U01DK086816)
1710-P

Targeted Metabolomics Identifies Elevated Serotonin Levels in Carriers of a TCF7L2 Diabetes Risk Allele

ANDREAS LEHERER, AXEL MEULENDIEK, KATHRIN GEIGER, CHRISTOPH H. SAELY, EVA-MARIA BRANDTNER, JANINE EBERL, BARBARA LARCHER, ARTHUR MADER, PETER FRANZBACHER, HEINZ DREKEL, Tiefsen Liechtenstein Feldkirch Austria (BMI, Sex, and Ancestry). Significant (P<1.8×10^{-7}) vQTL and rQTL minor allele frequency >0.01, for rQTL and vQTL patterns in year one changes the DPP (n=1,762) we screened 280,965 exomic and intergenic SNPs with flagging G×G and G×E interactions. In the metformin and placebo arms of occur when the variance of a glycemic trait varies by genotype (potentially correlation between multiple glycemic traits varies by genotype and vQTL tify genetic markers for G×E and G×G, we screened individual markers for RESEARCH GROUP,

1711-P

Quantitative Trait Loci GxE and GxG for Glycemic Traits—Response to Metformin and Placebo in the Diabetes Prevention Program (DPP)

TAYLOR J. MAXWELL, KATHLEEN A. JABLONSKI, PAUL W. FRANKS, STEVEN E. KAHN, WILLIAM C. KNOWLER, KIERN J. MATHER, JOSE C. FLORENZ, DPP RESEARCH GROUP, Ashburn, VA, Rockville, MD, Malvern, Swindon, Seattle, WA, Phoenix, AZ, Indianapolis, IN, Boston, MA

The complex genetic architecture of type 2 diabetes (T2D) includes gene-by-environment (GxE) and gene-by-gene (GxG) interactions. To idenfity genetic markers for GxE and GxG, we screened individual markers for patterns indicative of interactions (rQTL and vQTL). rQTL exist when the correlation between multiple glycemic traits varies by genotype and vQTL occur when the variance of a glycemic trait varies by genotype (potentially flagging GxE and GxG interactions). In the metformin and placebo arms of the DPP (n=3704) we screened 280,965 exomic and intergenic SNPs with minor allele frequency >0.01, for rQTL and vQTL, patterns in year one changes from baseline in glycemic traits (insulinogenic index (IGI), insulin sensitivity index (ISI), fasting glucose and fasting insulin). Covariates included baseline age and BMI, sex, and ancestry. Significant (P<1.8×10^{-10}) vQTL and rQTL generated a priori hypotheses for GxE screens and individual GxG tests for a SNP × metformin treatment interaction. All P values were obtained via parametric bootstrapping. Several unique vQTL and rQTL were identified, leading to E nominally significant metformin treatment × SNP interactions (4 IGI, 1 insulin, 1 glucose) and 12 GxE interactions (all IGI) that exceeded experiment-wise significance (P<6.6×10^{-5}). Of these loci, some are directly associated with incident diabetes, others act as rQTL to modify a glycemic trait’s risk relationship with diabetes (2 diabetes/glucose, 2 diabetes/insulin, 1 diabetes/IGI). rs3197699, an IGI, is possibly a gene damaging missense mutation in MST1, a gene affecting β-cell apoptosis and insulin secrerion that in DPP and other studies is associated with diabetes and other glycemic traits. This rQTL may also link MST1 with insulin sensitivity where IGI and insulin responses differentially vary by genotype. This study demonstrates evidence for context-dependent effects (GxG) and GxG and complex- ity of these T2D-related traits.

1712-P

Ancestral Differences in Hemoglobin A1C (A1C) Associations of Erythrocytogenetic Genes Using NHLBI Trans-Omics for Precision Medicine (TOPMed) Whole Genome Sequence (WGS) Data

CHLOE SARRONISKIS, AARON LEUNG, LAURA RAFFIED, TOPMED DIABETES WORKING GROUP, Boston, MA, Chapel Hill, NC

The latest transethnic genome-wide association study on A1C identified 22 loci that modify A1C independently of glycemia. These loci overlap genes implicated in erythrocyte phenotypes that vary in prevalence across popula- tions. We used TOPMed WGS data to estimate ancestral differences in associations with A1C at these loci and 23 additional erythrocyte genes not previously known to be related to A1C.

We conducted WGS association analyses of A1C in 5224 nondiabetic individuals (2862 European ancestry (EA); Framingham Heart Study and Amish, 2562 African ancestry (AA): Jackson Heart Study) using age and sex-adjusted linear mixed-effect regression, and meta-analyzed cohort-specific results. We used Cochran heterogeneity and Fisher’s exact tests to assess ancestral differences in effect and Minor Allele Frequency (MAF).

We detected single variant associations in 11 genes/loci (P<0.001; α = 0.05/46; ±1 cohort, Table). Variants had ancestral differences in MAF (P< 1%) and ancestry-specific signals (EA: GBDP, HBB, HBAT; AA: ANK1, PIEZO1, SPTA1, SPTB, HBAA). Genetic variation at erythrocyte genes exhibit ancestral differences in A1C effect and MAF. These variants may differ in their contributions to individual A1C variation, which may impact glucose estimation and diabetes diagnosis by A1C, particularly in minority populations.

Table.

1713-P

Genome-Wide Study of Inflammatory Cytokines in Southwestern Native Americans Identifies Novel Association Between WWOX and Serum TNF-x Levels

LAUREN E. WEDIKIND, MARY WALTER, SAYUKO KOBES, PENG CHEN, WENCHI HSUEN, ROBERT NELSON, LESLIE BAIER, WILLIAM C. KNOWLER, ROBERT L. HANSON, Phoenix, AZ, Bethesda, MD

Inflammatory processes may contribute to type 2 diabetes (T2D), but there is limited information about genetic associations with circulating levels of inflammatory cytokines. We performed a genome-wide association study (GWAS) of cytokines in 1061 nondiabetic Southwestern Native Americans (500 women; 561 men).

Fasting serum concentrations of interleukin-6 (IL-6), plasminogen activa- tor inhibitor-1 (PAI-1) and tumor necrosis factor-x (TNF-x) were measured using EMD Millipore assays. Genotypic data on 496,190 single-nucleotide polymorphisms (SNPs) with minor allele frequency ≥1% and ancestry-specific signals (AA: GBDP, HBB, HBAT; EA: ANK1, PIEZO1, SPTA1, SPTB, HBAA). Genetic variation at erythrocyte genes exhibit ancestral differences in A1C effect and MAF. These variants may differ in their contributions to individual A1C variation, which may impact glucose estimation and diabetes diagnosis by A1C, particularly in minority populations.

Table.
insulin response to intravenous glucose (β = 20% decrease per G allele copy, p = 0.045).

This study identified a novel association for TNF-α levels at WWOX (a gene previously implicated in T2D and insulin secretion in Han Chinese study populations) and suggests potential genetic links between inflammation and insulin secretion.

1714-P

CRISPR Mediated Deletion of a Proxy 19.2kb Distal to the T2D GWAS-Implicated SLC30A8 Region: Variant Impacts RAD21 and UTP23 Gene Expression in HepG2 Cells

KENYVITA M. HODGETS, SUMMI LI, MICHELLE LEONARD, JAMES A. PIPPIN, ALECSANDRA CHESI, ANDREW D. WELLS, MATTHEW JOHNSON, STRUAN F. GRANT, Philadelphia, PA

Genome wide association studies (GWAS) have revealed multiple loci for type 2 diabetes (T2D). However, given that GWAS generally only reports genomic signals associated with a given trait, there is need for follow-up characterization. Despite key reports of missense variants within SLC30A8 conferring protection of T2D risk, there is still need to better understand the relationship between the GWAS signal and mechanism at this locus. The application of ‘Assay for Transposase Accessible Chromatin combined with sequencing’ (ATAC-seq) to Endo-BH, SGBS and HepG2 cell lines, representing models for pancreatic beta-cells, adipose and liver respectively, allowed us to filter for putatively informative proxy SNPs (r2>0.8) coinciding with open chromatin at this locus. Following sequencing on the Illumina Hi-Seq platform, the sentinel SNP itself coincided with open chromatin. Sequence data were compared to the reference genome, namely rs13286634 (a missense R325W variant), in both Endo-BH and SGBS; however, in HepG2 this region was closed while proxy rs9650069 was open, situated 3’ to SLC30A8 and 19.2kb from rs13286634. We elected to generate CRISPR/Cas9 mediated deletions immediately around rs9650069 in a mixed cell setting and thus the impact of this deletion on this gene could not be assessed. This effort implies an enhancer element for these genes in a liver cell model as being a part of the machinery genetically controlling this locus.

Supported By: National Institutes of Health (R21HD089824)

1715-P

A Comprehensive Type 1 Diabetes Genetic Risk Score Is Associated with Type 2 Diabetes in the Framingham Heart Study

SHYLAJA SRINIVASAN, AARON LEONG, MIRIAM UDLER, BIANCA C. FORNEAL, JAMES B. MEIGS, STEPHEN S. RICH, JOSEE DUPUIS, San Francisco, CA, Boston, MA, Charlotte, North Carolina

It is often difficult to distinguish between type 1 (T1D) and type 2 diabetes (T2D), particularly in young adulthood. Both T1D and T2D have significant genetic contributions to risk and understanding their genetic overlap may offer clinical insight. We examined whether a T1D genetic risk score (GRS) is associated with clinical features and diagnosis of T2D in the Framingham Heart Study (FHS).

We constructed a T1D GRS based on 79 SNPs from fine mapping results, with SNPs weighted by published effect sizes. The GRS included both HLA (27 SNPs) and non-HLA (52 SNPs) regions, and was applied to 1503 participants with T2D. Multivariate regression models assessed the association of the GRS with age at T2D onset, BMI, HbA1c, HOMA-β and HOMA-IR at the exam of diagnosis. Case-control analysis of 1503 cases and 5649 controls was done using multivariate generalized estimating equations (GEE) logistic models to determine the association between the T1D GRS and T2D risk with age and sex as covariates.

In FHS participants, the mean age at T2D was 57.2 years, BMI was 30 kg/m², and HbA1c 6.05%. The T1D GRS was not associated with T2D age of onset, or BMI, HbA1c, HOMA-β and HOMA-IR after excluding participants on medications for T2D. There was a trend towards lower HOMA-β and HOMA-IR values in the top quintile of the GRS (n=244, mean±2.47, SD: 0.7 for ln(HOMA-β) and mean±2.99, SD: 0.8 for ln(HOMA-IR)) when compared to the lowest quintile of the GRS (n=260, mean±2.53, SD: 0.8 for ln(HOMA-β) and mean±2.92, SD: 0.8 for ln(HOMA-IR)). The T1D GRS was associated with T2D (β = 0.06 per SD increase in GRS, SE = 0.03, OR =1.1, P = 0.04). When the non-HLA and HLA components of the GRS were tested separately, the results remained significant only for the non-HLA T1D GRS (β = 0.08 per SD increase in GRS, SE = 0.03, OR=1.1, P = 0.02).

A T1D GRS of non-HLA SNPs is associated with T2D in the FHS participants. Our further analysis with increased sample size in multi-ethnic populations may refine the impact of the T1D GRS to characterize individuals with T2D.

1716-P

Heme Deficiency Causes Impaired Glycogen Synthesis in Skeletal Muscle Leading to Insulin Resistance

OSAMU NAKAJIMA, SHINICHI SATOH, TOMOHIRO KIMURA, TSUKASA OSAKI, KELLY P. VINCENT, KIYAMU TAKAHASHI, TOHRU TANAKA, MIYU NAKAMURA, JIMA, Yamagata, Japan, Dublin, Ireland, Tokyo, Japan

In vertebrates, the initial step in heme biosynthesis is the production of 5-aminolevulinic acid (ALA) by ALA synthase (ALAS). The ALAS1 gene encodes a ubiquitously expressed isozyme. Mice heterozygous null for ALAS1 (A1+/-) experience mitochondrial dysfunction in skeletal muscle, impaired glucose tolerance (IGT) and insulin resistance (IR) past 20-weeks of age (aged A1+/-s). IGT/IR in aged A1+/-s was remedied by oral administration of ALA for 1-week. By contrast, mitochondrial dysfunction required 6-weeks of ALA administration before improvements could be observed, indicating the phenotype of IGT/IR is not due to mitochondrial dysfunction. We found no remarkable change in expressions and phosphorylation of proteins related to insulin signalling such as Akt and GSK3β in skeletal muscle of aged A1+/-s. Rather, abnormal ultrastructure of glycogen granules and increased glycogen contents were observed in muscle of aged A1+/-s, unlike of less than 15-weeks-old A1-/-s, and those abnormalities of glycogen were reversed after ALA-treatment for 1-week as well as IGT/IR.

The quantification of glycogen contents showed that insulin-induced glycogen synthesis was impaired in skeletal muscle of aged A1+/-s, and the reduced de novo glycogen synthesis was recovered in ALA-administered aged A1+/-s. Glycogen synthase (GS) activities were constitutively activated even at the low concentration of glucose 6-phosphate (G6P) and not augmented at the high concentration of G6P in extracts from skeletal muscle of aged A1-/-s, suggesting that GS fails to respond to allosteric activation by G6P. While, GS activities were normally regulated in those of ALA-administered aged A1+/-s. Taken together, our data suggest that impaired de novo glycogen synthesis in skeletal muscle is relevant to IGT/IR in aged A1+/-s due to constitutively activated GS without allosteric activation by G6P.

Ref. 1) Saitoh et al. PLOS ONE in press.

1717-P

SNP x SNP Interactions Elucidate TCF7L2′s Physiology Conveying Incretin Action

BENJAMIN JAGHTEHR, MARTIN HENI, STEFAN Z. LUTZ, HARALD STAIGER, ANDREAS PETER, HANS-ULRICH HAERING, ANDREAS FRITSCHE, ROBERT WAGNER, Tübingen, Germany

Introduction: Genetic polymorphisms in TCF7L2 are the strongest common risk variants for type 2 diabetes. We and others had showed that genetic variation in TCF7L2 affects incretin-stimulated insulin secretion. A recent genome-wide association study identified strong associations with incretin levels. We hypothesized that these SNPs interact with the well-known TCF7L2 variant rs7903146 on insulin secretion due to their incretin altering effect.

Methods: Insulin secretion was measured with OGTT-based indices that were calculated from insulin, C-peptide and glucose levels in the cross-sectional TUEF-cohort (n=2929). We also measured insulin secretion in a modified hyperglycemic clamp at 10 mmol/l, using additional GIP-1 infusion at the end of the clamp (n=76). Besides rs7903146 in TCF7L2, we genotyped rs17681684 in GLP2R, rs1800437 in GIPR, rs17683011 in SLC5A1, as well as 3 additional variants associated with GIP levels.

Results: Four of the 6 incretin-associated SNPs exhibited at least nominally significant SNP x SNP interactions with rs7903146 in TCF7L2 on insulin secretion measured by the corrected insulin response (CIR). In the hyperglycemic clamp study, rs7903146 in TCF7L2 interacted with rs1800437 in GIPR on both AUC insulin and C-peptide, and rs17683011 in GIP2R on AUC C-peptide during the GLP-1 stimulation phase (p<0.05).

Conclusion: These findings corroborate the role of the TCF7L2 variant in mediating incretin action to increase diabetes risk. They highlight the importance of SNP x SNP interactions in the assessment of the genetic architecture of type 2 diabetes.

Supported By: German Federal Ministry of Education and Research (0109295)
1718-P Effects of Aerobic and Resistance Training on Circulating Micro-RNA Expression Profile in Subjects with Type 2 Diabetes

DEBORÁ OLÍSO, MARCO DAURIZ, ELISABETTA BACCHI, CARLO NEGRI, ENZO BONDURA, PAOLO MUGGETTI, Venona, Italy

Structured exercise programs are of great benefit in order to obtain a proper glycemic control in subjects with type diabetes (T2D). However, whether the metabolic effects of aerobic (AER) and resistance (RES) exercise exert specific changes in the expression profile of circulating miRNAs (c-miRNAs) is still largely unknown. We studied 24 individuals with T2D from the RAED2 Trial (NCT01192049), randomly assigned to AER or RES training protocols (N=12; N=12). Firstly, the baseline and post-training levels of 179 c-miRNAs were measured by RT-qPCR in 6 individuals (N=3; N=3). Nineteen c-miRNAs exhibited at least 20% fold-change variation from baseline and were therefore measured in the whole group. Compared to baseline, the expression levels of miR-423-3p, miR-451a and miR-765-3p resulted significantly upregulated after exercise, irrespective of exercise type (P < 0.05). miR-451a and miR-423-3p changes were positively correlated with fat loss after correction for age, sex, BMI and hemoglobin A1c. However, only miR-451a eventually survived as predictor of fat loss after training (rho=0.45 and 0.43, respectively; P < 0.05). Both miRNAs, intriguingly, miR-451a and miR-766-3p resulted associated with methylation of the C-allele at SNP-420. In conclusion, physical exercise in individuals with T2D is associated with specific changes of c-miRNAs profile, predominantly clustered along pathways with regulatory significance for fatty acid metabolism. Further investigations are warranted to confirm our findings and to unravel their mechanistic significance.

1719-P Association of CREBRF Variants with BMI and Diabetes in Pacific Islanders

ROBERT L. HANSON, SAIED SAFAKASHKH, JEFFREY CURTIS, DARIN K. MAHKEE, LESA BAILEY, WILLIAM C. KNOWLER, ROBERT NELSON, WEN-CHI HSUEH, Phoenix, AZ, Sinajana, Guam

A recent genome-wide association study (GWAS) in Samoans (a Polynesian population) identified strong associations of CREBRF variants with BMI. The G allele at rs15135649 (frequency=25.8%) was associated with ~1.3 kg/m2 higher BMI per copy, as was the Gln allele at rs373863828 (which codes for an ArgGln substitution). The Gln allele at rs373863828 was ~0.8 cm shorter in people carrying the Gln allele at rs373863828, and the Gln allele at rs373863828 was associated with lower risk of type 2 diabetes [T2D, odds ratio (OR)=0.62, P=0.006 and OR=0.45, P=0.001]. When stratified by BMI and T2D status, both alleles were associated with lower BMI in the C/C genotype (OR=0.8 cm, P=0.11, and OR=1.5 cm, P=0.019). The alleles conferring higher BMI were associated with lower risk of T2D (OR=0.67, P=2.9×10-8). These results suggest that CREBRF is evolutionarily conserved among many species. Several prediction software tools suggested a deleterious effect of the L475P mutation. This L475P mutation is a target recruitment subunit of an E3 ubiquitin ligase complex, which plays an important role in degradation of cyclinB1 - a regulatory protein involved in mitosis. Suppression of ZYG11A in 11B progenitor cells by specific small interfering RNA (siRNA) significantly reduced cell proliferation (p = 0.001) while increased cyclinB1 protein levels (p = 0.001). Moreover, 1.1B progenitor cells over-expressing ZYG11A showed a significant increase in proliferation as compared to the control cells (p = 0.01) whereas this effect was not observed in the cells overexpressing the mutant ZYG11A (p = 0.659). Taken together, this finding demonstrates the crucial role of ZYG11A in J-cell cycle regulation. It also suggests heterozygous ZYG11A-L475P mutation as a cause of MODY in the Thai family studied.
The development and progression of insulin resistance is driven by genetic and environmental factors and their interactions. Sucrose belongs to nutrition factors with lipogenic impact, induces de novo lipogenesis, reduces fatty acid oxidation and can deteriorate insulin sensitivity. The aim of study was to investigate transcriptome profile in adipose and muscle tissues under standard or high sucrose diet (HSD) (70 kcal% as sucrose) in two strains of rats—Wistar and a strain of hereditary hypertriglyceridemic rats (HHTg) as a polygenic model of metabolic syndrome and insulin resistance. The transcriptome analysis was evaluated in the context of development and progression of insulin resistance. HSD feeding in 2 weeks increased epididymal adipose tissue (EAT) weight in both strains (P diet<0.05), but not body weight. In addition, HSD feeding resulted in elevated levels of fasting glucose (P diet<0.05), insulin (P diet<0.01) and FFA (P diet<0.05, P strain<0.05), but adiponectin was decreased only in HHTg rats (P<0.01). Insulin sensitivity of EAT was significantly reduced (P diet<0.05, P strain<0.05), but HSD did not change triglycerides or insulin sensitivity in muscle. In skeletal muscle, HSD significantly changed expression (FDR<0.05) of 20 transcripts in HHTg and 21 in Wistar (only 2 common). In EAT, HSD significantly changed expression of 810 transcripts in HHTg and 1823 in Wistar (344 common). The most affected pathways were insulin receptor signaling in HHTg and mitochondrial dysfunction and oxidative phosphorylation in Wistar rats. Major regulator nodes of the mechanistic networks included insulin, SCD and miR-27 for HSD effect in HHTg and LP, miR-27 and VEGF in Wistar strain.

In conclusion, HSD feeding impaired insulin sensitivity in both rat strains. Transcriptomic alterations in adipose tissue precede muscle changes caused by HSD and show distinct patterns in genetically susceptible HHTg model of metabolic syndrome.

Supported By: Ministry of Health of the Czech Republic (N00023001)

Hepatic Transcriptional Signature of High-Sucrose Diet in Non-obese Model of Metabolic Syndrome and Prediabetes

IRENA MARKOVA, MARTINA HUttl, HANA MALINSKA, ONDREJ SEDA, LUDMILA KAZDOVA, Prague, Czech Republic

Both genetic predisposition and nutrition factors, such as high sucrose diet (HSD), are involved in the development of metabolic syndrome and insulin resistance. HSD can cause glucose intolerance and liver steatosis and exert hypertriglyceridemic effect. The aim of this study was to investigate the liver transcriptome profile under standard diet or HSD (70 kcal% as sucrose) in two strains of rats. We used Wistar rats and a strain of hereditary hypertriglyceridemic rats (HHTg) as a polygenic model of metabolic syndrome and insulin resistance. HSD feeding in 2 weeks did not affect body weight, but fasting glucose and AUC were increased (P diet<0.01, P strain<0.05). HSD feeding in both strains led to marked accumulation of hepatic triglycerides (P diet<0.01). However, cholesterol concentrations in the liver were reduced after HSD (P diet<0.01) in both strains. Comparative transcriptomic analyses in the liver identified (FDR<0.05) sets of differentially expressed genes in response to HSD common to both strains (n=595 transcripts) as well as HHTg (n=887) and Wistar (n=1531) specific sets. Network analysis revealed over-representation of genes involved in transport, synthesis or regulation of lipid metabolism (SREBF, PPARA, PPARG, SCD), mitochondrial dysfunction, excessive oxidative stress response (NRF2-mediated) and endoplasmic reticulum stress. Expression of genes related to sterol biosynthesis and oxidative phosphorylation was down-regulated, whereas genes involved in fatty acid synthesis (FAS, ACC), oxidative or endoplasmic reticulum stress were up-regulated after HSD. Our results support that HSD induced alterations in the liver transcriptome in both strains, which precede the development and progression of liver steatosis. The top regulated gene networks included lipid metabolism and mitochondrial dysfunction. Most of the major expression shifts due to HSD were similar in direction in both strains but differed in magnitude of expression change.

Supported By: Ministry of Health of the Czech Republic (N00023001)

No Evidence of a Causal Association between Diabetes-Related Phenotypes and Atrial Fibrillation

HADI HARATI, DANIELA ZANETTI, ERIK INGELSSON, JOSH KNOWLES, Palo Alto, CA, Stanford, CA

Background: Several epidemiological studies have shown an association between increased fasting and 2-hour plasma glucose (FFG and 2hFG), hemoglobin A1C (A1C), and fasting insulin (FI) and risk of atrial fibrillation (AF). We aimed to assess whether this relation is causal using genetic data from large populations of individuals of European descent.

Methods: Two-sample Mendelian randomization (MR) was used to obtain estimates of influence of the risk factors (FFG, 2hFG, A1C and FI) on risk of the outcome (AF). Instrumental variables (IVs) were constructed using previously reported single nucleotide polymorphisms (SNPs) associated with each risk factor at p-value<8 e-8 from the Meta-Analyses of Glucose and Insulin-related traits Consortium ( MAGIC) with up to 133,000 nondiabetic participants. SNPs were checked for pleiotropy using the UK Biobank dataset and those associated with the confounders at p-value<8 e-8 were excluded. AF consortium (AFlagen) summary statistics with 22,346 AF cases and 132,086 controls was used for the outcome data analysis.

Results: Two-step MR with inverse variance weighted methods did not show any causal association between diabetes related phenotypes and AF (FFG (30 SNPs, p=0.1), 2hFG (7 SNPs, p=0.3), A1C (11 SNPs, p=0.3), or FI (13 SNPs, p=0.9)). None of the IVs showed horizontal pleiotropy indicating that the used genetic variants affected the outcome only via their effect on the diabetes related phenotypes (p-values of 0.56, 0.09, 0.099, and 0.31 respectively for FFG, 2hFG, A1C, and FI). Calculated power based on the original set of SNPs in the MAGIC and estimated odds ratio of 1.2 was 99, 94, 99, and 84% respectively for FFG, 2hFG, A1C, and FI.

Conclusion: This MR analysis does not support a causal role between genetically programmed diabetes related traits (FFG, 2hFG, A1C, or FI) and AF. These data suggest that drug treatment to reduce dysglycemia in non-diabetics may not be an effective strategy for AF prevention.

Supported By: National Institutes of Health
Type 2 diabetes (T2D) is associated with chronic low-grade inflammation. We studied its mechanisms by addressing the role of inflammasomes in monocytes and their activation by circulating metabolites to produce inflammatory cytokines IL1β and IL18. Blood samples were collected from patients with T2D. Serum was filtered at 3 kDa to remove macromolecules. Inflammasome activation was analyzed by gene expression of various Nod Like Receptors by RT-quantitative PCR as well as IL1β and IL18 secretion from these monocytes in culture (ELISA). Twenty-one patients (38% women) were included in 2018. They were 57±10 years old, BMI were 33.1±6.3 kg/m². They had T2D for 14±9 years and HbA1c at 9.5±1.2%. Their C Reactive Protein levels was 8.1±8.0 mg/L. Each subject was sampled twice at 4 days of interval: in normoglycemia (2.56±0.89g/L) then in hyperglycemia (1.23±0.41g/L). Two inflammasomes were transcripted: NLRP1 and NLRC4, with significant high level whether in normoglycemia (fold-change 1.47, p=0.01 and 1.33, p=0.02) and hyperglycemia (fold-change 1.41, p=0.02 and 1.31, p=0.04). This transcriptional priming seems to have a functional consequence with IL1β production by monocytes of some T2D patients. Healthy monocytes were collected from voluntary blood donors (Glycaemia: 0.97±0.17g/L). Incubation of them with filtered serum of T2D patients recapitulated the priming signal. The same two inflammasomes were transcripted: NLRP1 and NLRC4, whether in normoglycemia (fold-change 1.35, p=0.002 and 1.23, p=0.02) and hyperglycemia (fold-change 1.31, p=0.01 and 1.30, p=0.052). Although it did not induce activation of mature cytokines. We have shown the activation of NLRP1 and NLRC4 inflammasomes and their secretion of inflammatory cytokine in T2D patients. Some soluble serum metabolites seem directly involved in this inflammatory cascade. Our next objective will be to identify these molecules, which are potential biomarkers of predictive of chronic immune activation in T2D.

Supported By: Société francophone du diabète
Pharmacological Inhibition of Neutrophil Elastase Attenuates Insulitis and Autoimmune Diabetes in Mice
SHU LINGLING, LING ZHONG, RLC HOO, AIMIN XU, Hong Kong, China

Background: Type 1 diabetes is an autoimmune disease resulted from self-destruction of insulin-producing pancreatic beta-cells. However, the pathological pathways that trigger the autoimmune destruction remain poorly understood. Our previous studies demonstrated that increased circulating neutrophil elastase (NE) is closely associated with beta-cell autoimmunity in patients with T1D. Here we investigate the role and mechanism whereby NE participates in the pathogenesis of T1D, and explore the therapeutic potential of the pharmacological NE inhibitors for autoimmune diabetes.

Method: Biochemical and immunological analysis were adopted to determine the dynamic change in the infiltration and activation of neutrophils in pancreas of NOD mice. NE-specific endogenous (pre-elafin/elafin) or pharmacological (sivelustat) inhibitors were supplemented into NOD mice to evaluate their effects on diabetes incidence and insulinitis. Flow cytometry was employed to explore the effects of NE in mediating the crosstalk of immune cells.

Results: A dynamic change in the infiltration of neutrophils was observed in pancreatic islets of NOD mice, leading to a transient elevation of local NE activity. Supplementation of NE-specific inhibitors rectified the elevated pancreatic NE activity, alleviated insulinitis and reduced the development of T1D in NOD mice. Inhibition of NE activity significantly attenuated the infiltration of pro-inflammatory macrophages into pancreatic islets, reduced the production of inflammatory cytokines. In vitro studies showed that NE directly induced inflammatory responses in both min8 beta-cells and RAW264.7 macrophages through the activation of TLR4-α-IκB pathway.

Discussion: NE-mediated crosstalk between beta-cell and macrophages forms a vicious feedback loop, resulting in the exaggerated beta-cell damage in NOD mice. Pharmacological inhibition of NE may represent a promising therapeutic strategy for treatment of autoimmune diabetes.

Supported By: Research Grants Council of Hong Kong (RGC17128115)

The MultiPepT1Dex Study—Examining the Safety of Peptide Immunotherapy Using Multiple Islet Antigens in Recent-Onset Type 1 Diabetes
YUK-FUN LIU, JAKE K. POWRIE, SEFINA ARIF, NIKOLAOS FOUNTALIKIS, MAMTA JOSHI, EMMA L. SMITH, FOIETINI STRIMENOPOLI, MOIRA THOMSON, MARK PEARKMAN, London, United Kingdom, Slough, United Kingdom

Background: Peptide immunotherapy (PIT) aims to modulate immune responses to specific antigens in order to restore immune tolerance. Recently, we reported outcomes of a phase 1b study of PIT at type 1 diabetes onset, showing safety, tolerability and changes in immune regulation pathways, following up to 12 doses of 10µg of a single proinsulin peptide that is naturally processed and presented by HLA-DR4 (DQB1*0401). Preclinical PIT studies show that multiple peptides in combination enhance tolerance induction.

Aims: To evaluate the safety and clinical effects of PIT using a mix of multiple islet autotigands peptides in adults with recent-onset type 1 diabetes.

Methods: The MultiPepT1Dex study was a single centre, double-blind placebo-controlled, ascending dose, randomized trial recruiting adults aged 18-45 years within 4 years of diagnosis with HLA-DRB1*0401 genotype, positive islet autoantibodies and stimulated C-peptide ≥0.2pmol/L. Study drug comprised of 8 naturally processed and presented, islet-derived peptides (MultiPepT1Dex). Participants were enrolled into 3 cohorts for monthly intradermal injections for 6 months. In each cohort, subjects were randomised to receive placebo (n=2) or MultiPepT1Dex (n=6) at 10µg (Cohort 1) or 50µg (Cohort 2) or 500µg (Cohort 3) dose.

Results: Twenty-seven participants were randomized; 3 participants withdrew for non-clinical reasons and were replaced. There were no episodes of systemic hypersensitivity, anaphylaxis or serious adverse reactions linked to MultiPepT1Dex administration. Analysis of changes in stimulated C-peptide, HbA1c and insulin dose per kg showed no evidence of disease acceleration following dosing compared with placebo. Mild transient injection site erythema was observed in all cohorts, with no increase on repeated dosing.

Conclusions: Intradermal administration of multiple islet-derived peptides up to a cumulative dose of 3000µg is well tolerated with no safety concerns.
A novel cell-based cAMP assay can be extended to high-throughput (pM vs. nM), and shorter procedure time (hours vs. days). Thus, applications low matrix effect with wide assay window (5 fold higher), high sensitivity ELISA-based assay, this assay requires less sample volume (20ul vs. 100ul), nominal RP was >0.99 and the recovery of the expected relative potency in and ELISA. Over the 8 weeks, 6 ulcers healed (H) and 15 failed to heal (NH).

Change in Circulating Monocyte Profile with Foot Ulcer Healing in Diabetic Patients

DANGING MIN, VANESSA L. NUBE, ANH TAO, YIN YUAN, BELINDA BROOKS, YOICHI OIKAWA, TAKESHI KATSUKI, TOSHIHIDE KAWAI, AKIRA SHIMADA, SATAMA Japan, Tokyo, Japan

We previously demonstrated that patients initially diagnosed with slowly progressive insulin-dependent (type 1) diabetes mellitus (SPIDDM) using a radioimmunooassay (RIA) test for anti-glutamic acid decarboxylase antibody (GADA) (GADA-RIA), who were also positive on a GADA enzyme-linked immunosorbent assay (ELISA) test (GADA-ELISA), showed a reduced insulin secretory capacity early in the SPIDDM disease process (Endocr J. 2017;64:163). When we used GADA-RIA test, in SPIDDM with non-insulin dependent state, a GADA-RIA value ≥10 U/mL (GADA-RIA-High) was believed to indicate a higher risk for future insulin dependency than a value <10 U/mL (GADA-RIA-Low). In our previous study also, the insulin secretory capacity may be lower in “GADA-RIA-High” and GADA-ELISA-positive SPIDDM patients” (A group) than those with “GADA-RIA-Low and GADA-ELISA-positive SPIDDM patients” (B group) early in the disease process, but this point was not yet confirmed. Therefore, we have now performed additional analysis to compare serum C-peptide levels in these two patient groups (group A vs. B). When restricted to a shorter disease duration, <11 years based on our previous study, serum C-peptide levels were 0.73 ± 0.61 ng/mL in group B (n = 9) and 0.88 ± 0.65 ng/mL in group A (n = 15). There was no significant difference between the two measures, but each of these two measurements was significantly lower than those for patients with type 2 diabetes (2.0 ± 0.85 ng/mL, n = 15) and “GADA-RIA-Low and GADA-ELISA-NEGATIVE SPIDDM patients” (2.60 ± 1.66 ng/mL, n = 6). These findings suggest that, regardless of their GADA-RIA titer, GADA-ELISA-positive patients with SPIDDM may show a reduced insulin secretory capacity early in the disease process. In conclusion, unlike GADA-RIA test, a cut-off value for GADA-ELISA test for predicting future insulin dependency in SPIDDM may not exist.

Mucosal Gamma/Delta T Cells Increased by i.n. Administration of Gliadin to 4-week-old NOD Mice Prevent Diabetes in the NOD-SCID Model of Adoptive Cotransfer of Diabetes

DAVID FUNDA, JAROSLAV GOLIAS, MARTIN HAUPT-JORGENSEN, KARSTEN SVENSSON, KARL-JOHN SODIN, THERESA BURON, ROBERT J. MULLER, MARKUS BITZER, OLA H. BRUUN, JAN MAK, GEORGE F. FORD, DAVID J. BLOCH, ANDREAS BÖTTCHER, ANDREW T. MURPHY.

Beta-cell autoantigens, e.g., insulin, proinsulin, or GAD65, have been investigated both in animal models and human trials for induction of beta-cell specific tolerance to prevent the development of type 1 diabetes (T1D). On the other hand, environmental factors that significantly contribute to the recent outbreak of T1D were less studied, probably due to their complexity. The dietary wheat protein fraction has been associated with high penetrance of the disease, whereas gluten-free diets prevented T1D in animal models. We have previously reported that i.n. administration of gliadin prevented diabetes in NOD mice. Herewith we investigated mucosal gamma/delta T cells that were induced by i.n. administration of gliadin for their regulatory capacity to prevent diabetes in the NOD-SCID model of diabetes co-transfer. i.n. administration of gliadin to 4-week-old NOD mice increased proportion of gamma/delta T cells in pancreatic and mesenteric lymph nodes. Adoptive co-transfer of 2x10^5 gamma/delta T cells with 1x10^7 diabetogenic splenocytes led to statistically significant (p<0.01) diabetes prevent-
immunology/transplantation

**1739-P**

### Glycolysis-Dependent Inflammasome Activation by Carbon Monoxide

**DAEYEON KIM, SUNG WAN CHUN, YEOJOO KIM, SANG JIN KIM, JONG-SEOK MOON, Cheonan DAEYEON KIM, SUNG WAN CHUN, YEOJOO KIM, SANG JIN KIM, JONG-SEOK MOON, Cheonan Republic of Korea**

Low dose of carbon monoxide (CO) has anti-inflammatory role through various signaling pathways. Cellular metabolism has been implicated in the activation of inflammation in immune cells.

Here we show that CO-dependent metabolic pathway regulates the activation of the nucleotide-binding domain, leucine-rich-repeat-repeat-containing receptor (NLR), pyrin-domain-containing 3 (NLRP3) inflammasome. CO-releasing molecule-3 (CORM-3) resulted in reduced glycolysis-dependent NLRP3 inflammasome activation in macrophages. The reduced mTORC1 activation by CORM-3 resulted in less glycolysis during NLRP3 inflammasome activation. CORM-3 suppressed caspase-1 activation and the secretion of IL-1β and IL-18 in macrophages in response to LPS and ATP. Moreover, CORM-3 inhibits the oligomerization of the adaptor protein apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), which is required for NLRP3-dependent caspase-1 activation. Furthermore, CORM-3-treated mice showed substantial reduction in IL-1β production by hyperglycemia in a mouse model of STZ-induced diabetes.

Our results suggest that CO regulates glycolysis-dependent NLRP3 inflammasome activation and may provide a therapeutic approach for inflammation in metabolic diseases.

**Figure.** CORM-3 Treatment Suppresses NLRP3 Inflammasome Complex Formation during NLRP3 Inflammasome Activation.

**Supported By:** Soonchunhyang University (NRF-2017R1C1B5017148)

---

**1740-P**

### Flash Glucose Monitoring Reflects Graft Function after Clinical Islet Transplantation—An Initial Report

**ANNA LAM, SHAREEN FORBES, CECILIA HAMMING, ANDREW J. MALCOLM, A.M. JAMES SHAPRO, PETER A. SENIOR, Edinburgh, AR, Canada Edinburgh, United Kingdom**

Metabolic assessment in clinical islet transplantation (CIT) has primarily been limited to the research setting. However, technological advances may now allow for this in routine practice. We describe here how flash glucose monitoring (FGM) in islet transplant recipients with varying degrees of graft function as assessed by BETA-2 score (validated clinical index, range 0-42).

In conclusion, similar to i.n. administration of insulin, i.n. vaccination with gliadin, an environmental antigen with possible etiological influence in T1D, led to increased proportion of mucosal gamma/delta T cells. These gamma/delta T cells possess regulatory capacity to prevent diabetes transfer in the NOD-SCID model and may represent a novel and safer strategy for prevention or an early intervention in T1D.

---

**1742-P**

### Pax4 Gene Transfer Induces α-to-β Transdifferentiation and Improves the Therapeutic Efficacy of Islet Transplantation

**KESHAB R. PARAJULI, YANQING ZHANG, HONGJU WU, New Orleans, LA**

Pax4 is a transcriptional factor which plays a critical role in the generation of insulin producing β-cells during embryonic development. Our group previously demonstrated that Pax4 delivered by adenoviral vector induces insulin expression and reduces glucagon in αT1.9 cells and primary human islets. The purpose of the present study was to determine whether Pax4 gene expression induces pancreatic α-cells to become β-cell using lineage tracing techniques and confers therapeutic benefits in the context of islet transplantation. In this study, we generated α mouse model in which their α-cells are

**Supported by:** National Institutes of Health
Development of Perfluorodecalin Contained Microcapsules for Islet Survival and Function
JINWON KIM, HEON SEOK PARK, KUN-HO YOON, EUN YOUNG LEE, Seoul, Republic of Korea

Hypoxic injury of islets is a major obstacle for encapsulated islet transplantation into the peritoneal cavity. To improve oxygen delivery to encapsulated islets, we integrated 20% of the oxygen carrier material, perfluorodecalin (PF) contained alginate capsules with islets (PFD-alginate). Integration of PF clearly improved islet viability and decreased reactive oxygen species production compared with islets encapsulated with alginate only (alginate) and naked islets exposed to hypoxia in vitro. In PFD-alginate capsules, HIF-1α expression was minimal, while insulin expression was much better secured. Furthermore, the best islet function represented by glucose-stimulated insulin secretion was observed for the PFD-alginate capsules. In vivo study, the marginal number of naked islets and encapsulated islets (alginate and PFD-alginate) were transplanted into streptozotocin-induced diabetic mice. Non-fasting blood glucose levels and intraperitoneal glucose tolerance tests in the PFD-alginate group were lower than in the alginate group. The harvested islets showed positive staining for insulin in all groups, but the ratio of dead cell area was 13% higher in the alginate group than in the PFD-alginate group.

In conclusion, PFD contained alginate microcapsules improved islet function and survival by minimizing the hypoxic damage of islets after intraperitoneal transplantation.

Synergistic Effect of Islet Magnetic Resonance Imaging Using Direct Linking of Ferumoxyl to Surface of PEGylated Islet
HAN SONG LEE, YOUNGSANG KWON, HYUNJIN KIM, MUHAMMAD R. HAQUE, KYU MIN JIN, MOON-KYU LEE, JAE HYEON KIM, Seoul, Republic of Korea

Purpose: We previously reported the feasibility of islet magnetic resonance imaging (MRI) using ferumoxyl, which is the only clinically-available ultraslim superparamagnetic iron oxide. However, the labeling efficacy was not sufficient for its clinical use in islet transplantation. We aimed to evaluate the feasibility of islet MRI using direct linking of ferumoxyl to islet surface through PEGylation.

Method: Islets were labeled by surface modification with up to 4% PEG-heparin-ferumoxyl. We compared islet function and viability of control islets and ferumoxyl-heparin-PEGylated islets. Efficacy of labeling with ferumoxyl-heparin-PEGylation and ferumoxyl alone was assessed in both ex vivo and in vivo models.

Results: Labeling of islets with up to 2% PEG-heparin-ferumoxyl did not derange ex vivo islet viability and function. The T2* relaxation time was optimal when islets were labeled with 1 to 4% PEG-heparin-ferumoxyl. The labeling intensity in the ex vivo MRI of ferumoxyl-heparin-PEGylated islets was stronger than islets labeled with ferumoxyl alone. In syngeneic renal subcapsular islet transplantation, labeling with ferumoxyl-heparin-PEGylation showed better in vivo labeling efficacy than that of islets labeled with ferumoxyl alone. After labeling with ferumoxyl-heparin-PEGylation, there was a correlation between the total area of visualized islets and the transplanted islet mass in syngeneic mouse intraportal islet transplantation, and the visibility was also confirmed in the preliminary analysis of non-human primate intraportal islet transplantation model.

Conclusion: Direct linking of ferumoxyl to islet surface through PEGylation improved the labeling efficacy and it could be used for the islet MRI in clinical islet transplantation.

Intraperitoneally Administered Neo-Islets, Aggregates of Mesenchymal Stem Cells, and Cultured Islet Cells Improve Glycemic Control of Spontaneously Occurring Insulin-Dependent Diabetes Mellitus in Pet Dogs—a Pilot Study, INAD 012-776
CHRISTOF WESTENFELDER, ANNA GÖÖCH, NATASHA K. LOY SON, NICOLE AVILA, JULIE R. FISCHER, Salt Lake City UT, San Diego, CA, San Marcos, CA

The clinical need for novel technologies that effectively treat patients with T1DM and render them insulin-independent is great. Endogenous insulin replacement by pancreas or islet transplants is currently the only treatment that can achieve insulin independence and provide significant end organ protection in patients with autoimmune-mediated T1DM. However, the shortage of pancreas donors and the need for repeated islet transplants, requiring up to five donors each, continue to limit the availability of these expensive therapies. Both transplant modalities depend on the permanent use of potentially toxic antirejection drugs. We previously reported that allogeneic, i.e. administered “Neo-Islets” (NI), composed of cultured islet cells coaggregated with high numbers of immunoprotective and cytoprotective Adipose Derived Stem Cells (ASCs) reestablished normoglycemia in autoimmune T1DM NOD mice without the use of encapsulation devices or immunosuppressive agents. With FDA guidance, we are currently testing this NI technology in a pilot study of insulin-dependent, spontaneously diabetic pet dogs by the i.p. administration of 2x10^6 NIs/kg bw to metabolically controlled (blood glucose, triglycerides) dogs under light anesthesia and ultrasound guidance. Dogs are continued on insulin as needed and are to be followed for 3 years for adverse events, glycemic control, insulin need. Two dogs have been treated. One has been followed for 6 months, the other for 3 months. While decreasingly insulin dependent with significantly improved glycemic control, no IgG response to the allogeneic NIs, no adverse events have been observed.

In conclusion, these data demonstrate that this novel technology is safe, feasible and holds promise for the treatment of dogs with insulin dependent DM, but that further protocol/dosing optimization is required.

Are Liver Cystic Lesions after Islet Transplantation Caused by Streptozotocine?
LUCIE KOSIČNOVÁ, ALZBEŤA PATIČOVA, EVA STICOVA, ALŽBĚTA VOLTÍŠKOVÁ, LENKA BARTONOVÁ, MONIKA CAHOVA, JAN KRIZ, Prague, Czech Republic

Introduction: Pancreatic islets (PI) transplanted (Tx) into the portal vein cause a permanent exposure of surrounding liver tissue to insulin in high concentration. There were published several papers pronouncing the hypothesis of a direct triggering effect of Tx PI on a development of focal morphological changes in liver tissue (tumors, cysts). At the same time, streptozotocine (STZ) was supposed to play a minor but not negligible role in this phenomenon.

Methods: Syngeneic pancreatic islets were transplanted into the healthy or diabetic (50mg/kg STZ) Brown Norway rats. Group A (n=5): healthy, Tx of 450 PI into the portal vein; Group B (n=7): STZ-diabetes, Tx of 450 PI into the portal vein; Group C (n=6): STZ-diabetes, Tx of 100 PI under the left kidney
INSULIN ACTION—ADIPOCYTE BIOLOGY

Moderated Poster Discussion: Fat Is Where Insulin’s Art (Posters: 1748-P to 1753-P), see page 18.

1749-P
Depletion of CD206-M2 Like Macrophages Promotes the Browning of the White Adipose Tissue
ALLAH NAVAZ, SHIHO FUJISAKA, ISAO USUI, KUNIMASA YAGI, TAKASHI NAGAWA, TONOSURO KADU, KAZUYUKI TOSHE, YOSHIKO IGARASHI, KEISUKE OKABE, KUMIKO SAEKI, TOYAMA JAPAN, SHIHTOPIA JAPAN, TOKYO, JAPAN
We have previously shown that CD206-M2 like macrophages constitute a microenvironment for adipocyte progenitors (APs), in a Tgfβ-dependent manner, to retain systemic insulin sensitivity by tuning the quiescence/proliferation balance of APs to adapt to changes in nutritional status. Previously we generated CD206ΔTIR transgenic mice and CD206-CreERT2/Tgfb1flox/flox (Tgfβ KO) mice to determine the role of CD206 M2-like macrophages a role of CD206+ cell specific Tgfβ1 respectively, in the APs proliferation. Previous reports have shown that M2-like macrophages play a key role in the browning of WAT via activation of type 2 cytokines production during cold exposure. These findings revealed the relationship between the occurrence of beige adipocytes and M2-like macrophage recruitment. In order to investigate the role of CD206 M2-like macrophages in the induction of browning into the WAT, we extended our study to see the browning phenomenon by using CD206ΔTIR and Tgfβ1 KO mice. Here, we show that depletion of CD206 M2-like macrophages promotes the browning of WAT. We report that cold stimulation resulted in the generation of smaller adipocytes, upregulation of UCP1 and CD137, a marker for beige progenitors, in the WAT of CD206-ablated mice. Flow cytometry analysis further confirmed enhanced beige progenitors in the WAT. Since blocking of Tgfβ is known to promote browning of the WAT. Mechanistically, we assume that enhanced browning into the WAT of CD206ΔTIR mice might be due to the deletion of Tgfβ1 from CD206-M2-like macrophages. Taken together, we concluded that CD206 M2-like macrophages induce the proliferation of beige progenitors in the WAT, which may serve as effective therapeutic tools for the prevention and treatment of obesity.

Supported By: Kobayashi Foundation

1750-P
Inhibition of PPARγ, Adipogenesis, and Insulin Sensitivity by MAGED1
QINGHUA WANG, JING TANG, XIAO GAO, HAI-BIN RUAN, NANTONG, CHINA; NAN-JING, CHINA; MINNEAPOLIS, MN
Adipocytes serve as critical integrators of energy balance and glucose homeostasis by storing excess energy to prevent ectopic fat accumulation in non-adipose tissues and by secreting various adipokines to modulate whole-body metabolism. Peroxisome proliferator-activated receptor-γ (PPARγ) is a master regulator of adipogenesis and a target of the thiazolidinediones (TZD) class of anti-diabetic drugs; therefore, identifying novel regulators of PPARγ action in adipocytes is essential for the future development of therapeutics for diabetes. MAG Family Member D1 (MAGED1), by acting as an adaptor for ubiquitin-dependent degradation pathways and a co-factor for transcription, plays an important role in neural development, cell differentiation, and circadian rhythm. Here, we showed that MAGED1 expression was downregulated during adipogenesis and MAGED1 inhibited preadipocyte proliferation and adipogenesis in vitro. Mechanistically, MAGED1 bound to PPARγ and suppressed the stability and transcriptional activity of PPARγ. Compared to wild type littermates, MAGED1-deficient mice showed increased levels of PPARγ protein and its target genes, more CD29+CD34+Sca-1+ adipocyte precursors, and hyperplasia of white adipose tissues (WATs) at young ages. Moreover, MAGED1-deficient mice developed late-onset obesity as a result of decreased energy expenditure and physical activity. However, these mice were metabolically healthy as shown by improved glucose clearance and insulin sensitivity. Lipid profiling showed that obesity in MAGED1 knockout (KO) mice did not cause increased levels of serum lipids. On the other hand, expression and secretion of adipokines such as leptin and adiponectin were upregulated in KO mice. Taken together, our data identify MAGED1 as a novel negative regulator of PPARγ activity, adipogenesis, and insulin sensitivity in mice. MAGED1 might therefore serve as a novel pharmaceutical target to treat obesity-associated insulin resistance.

Supported By: American Heart Association; Ministry of Science and Technology of China; National Natural Science Foundation of China

1751-P
Adipocyte EGFL6 Expression from Subcutaneous Adipose Tissue Alters Glucose Homeostasis and Affects Human Obesity
DAVID BRADLEY, ZHENG YIN, JOEY Z. LIU, ALECIA M. BLASZCZAK, STEPHEN T. WONG, WILLA HSHEU, COLUMBUS, OH, HOUSTON, TX
Recent data suggests that the adipose tissue (AT) extracellular matrix (ECM) may be a key player in the pathogenesis of obesity-related T2D. HFD feeding to collagen VI knockout mice reduces AT fibrosis (a hallmark of abnormal ECM) and improves insulin sensitivity despite an expansion of adipocyte volume. Endoplasmic reticulum factor-like-domain, multiple 6 (EGFL6) is a secreted protein best characterized for its role in tumor endothelial cell angiogenesis. Although previous studies have shown increased EGFL6 expression in whole fat of obese and insulin resistant subjects, its precise role in metabolic disease, the subtypes of cells within AT that overexpress EGFL6, and the mechanism(s) by which AT EGFL6 could modulate insulin sensitivity is unclear. Here, we report increased EGFL6 expression in human AT in young, obese type 2 diabetes (T2D) patients and in high fat diet (HFD) induced insulin resistant mice. Moreover, we show that AT EGFL6 can modulate angiogenesis, lipid metabolism, and adipogenesis in human AT. These findings may have important implications for novel therapeutic approaches to treat obesity and type 2 diabetes.

Supported By: American Diabetes Association (1-17-IBS-184 to Q.Y.); National Institutes of Health (RO1HL135333, RO5AG055889); University of Alabama at Birmingham (P30DK059336)
Insulin Action—Adipocyte Biology

Moderated Poster Discussion: Fat Is Where Insulin’s At (Posters: 1748-P to 1753-P, see page 18)

1748-P

Impaired Insulin Resistance in IF1-Deficient Mice Subjected to a High-Fat Diet with Reduced-Fat Mass and Skeletal Muscle Lipid Accumulation

FENG YUAN HUANG, KEVIN YANG, KAMALAMMA SAJA, YICHENG HUANG, QINGHUA WANG, JING TANG, XIANG GAO, HAI-BIN RUIAN, NANTONG CHINA, NAN-JING, CHINA, MINNEAPOLIS, MN

Adipocytes serve as critical integrators of energy balance and glucose homeostasis by storing excess energy to prevent ectopic fat accumulation in non-adipose tissues and by secreting various adipokines to modulate whole-body metabolism. Peroxisome proliferator-activated receptor-γ (PPARγ) is a master regulator of adipogenesis and a target of the thiazolidinediones (TZD) class of anti-diabetic drugs; therefore, identifying novel regulators of PPARα activity in adipocytes is essential for the future development of therapeutics for diabetes. MAGE Family Member D1 (MAGED1), by acting as an adaptor for ubiquitin-dependent degradation pathways and a co-factor for transcription, plays an important role in neural development, cell differentiation, and circadian rhythm. Here, we showed that MAGED1 expression was down-regulated during adipogenesis and MAGED1 inhibited preadipocyte proliferation and adipogenesis in vitro. Mechanistically, MAGED1 bound to PPARγ and suppressed the stability and transcriptional activity of PPARγ. Compared to wild type littermates, MAGED1-deficient mice showed increased levels of various adipokines and suppressed the expression of inflammatory genes. As a result, we observed increased levels of serum lipids and decreased glucose tolerance. These findings indicated the potential of MAGED1 as a novel negative regulator of PPARα activity, adipogenesis, and insulin sensitivity in mice. MAGED1 might therefore serve as a novel pharmaceutical target to treat obesity-associated insulin resistance.

Supported By: American Heart Association; Ministry of Science and Technology of China; National Natural Science Foundation of China

1750-P

Inhibition of PPARγ, Adipogenesis, and Insulin Sensitivity by MAGED1

QINGHUA WANG, JING TANG, XIANG GAO, HAI-BIN RUIAN, NANTONG, CHINA, NAN-JING, CHINA, MINNEAPOLIS, MN

We have previously shown that CD206+ M2-like macrophages promote the generation of beige progenitors in the WAT of CD206-DTR mice. In order to investigate the role of CD206 M2-like macrophages in the induction of browning into the WAT, we extended our study to see the browning phenomenon by using CD206-DTR and Tgfβ KO mice. Here, we show that depletion of CD206 M2-like macrophages promotes the browning of WAT. We report that cold stimulation resulted in the generation of smaller adipocytes, upregulation of UCP1 and CD137, a marker for beige progenitors, in the WAT of CD206-ablated mice. Flow cytometry analysis further confirmed enhanced browning in the WAT. Since blocking of Tgfβ is known to promote browning of the WAT. Mechanically, we assume that enhanced browning into the WAT of CD206-DTR mice might be due to the deletion of Tgfβ1 from CD206-M2-like macrophages. Taken together, we concluded that CD206 M2-like macrophages induce the proliferation of beige progenitors in the WAT, which may serve as effective therapeutic tools for the prevention and treatment of obesity.

Supported By: Kobayashi Foundation

1751-P

Adipocyte EGFL6 Expression from Subcutaneous Adipose Tissue Alters Glucose Homeostasis and Affects Human Obesity

DAVID BRADLEY, ZHENG YIN, JOEY Z. LIU, ALECIA M. BLASZCZAK, STEPHEN T. WONG, WILLA HSUEH, COLUMBUS, OH, HOUSTON, TX

Recent data suggests that the adipose tissue (AT) extracellular matrix (ECM) may be a key player in the pathogenesis of obesity-related T2D. HFD feeding to collagen VI knockout mice reduces AT fibrosis (a hallmark of abnormal ECM) and improves insulin sensitivity despite an expansion of adipocyte volume. Epidural growth factor-like-domain, multiple 6 (EGFL6) is a secreted protein best characterized for its role in tumor endothelial cell angiogenesis. Although previous studies have shown increased EGFL6 expression in whole fat of obese and insulin resistant subjects, its precise role in metabolic disease, the subtypes of cells within AT that overexpress EGFL6, and the mechanism(s) by which AT EGFL6 could modulate insulin sensitivity in mice. MAGED1 might therefore serve as a novel pharmaceutical target to treat obesity-associated insulin resistance.

Supported By: American Heart Association; Ministry of Science and Technology of China; National Natural Science Foundation of China

1749-P

Depletion of CD206 M2-Like Macrophages Promotes the Browning of the White Adipose Tissue

ALLAH NAJMI, SHISHI FUJISAKA, ISAO USUI, KUMIMASA YAGI, TAKASHI NAKAGAWA, TOSIMOSU KADO, KAZUYUKI TOBE, YOSHIKO IGARASHI, KEISUKE OKAIBE KUMIKO SAKEI, TOYAMA, JAPAN, SHIMOTOGA, JAPAN, TOKYO, JAPAN

We have previously shown that CD206 M2-like macrophages constitute a microenvironment for adipocyte progenitors (APs), in a Tgfβ-dependent manner, to retain systemic insulin sensitivity by tuning the quiescence/proliferation balance of APs to adapt to changes in nutritional status. Previously we generated CD206-ΔTDr transgenic mice and CD206-CreER/T2/Tgfβ1 Δflo/Δflo (Tgfβ1 KO) mice to determine the role of CD206 M2-like macrophages a role of CD206+ cell specific Tgfβ1 respectively, in the APs proliferation. Previous reports have shown that M2-like macrophages play a key role in the browning of WAT via activation of type 2 cytokines production during cold exposure. These findings revealed the relationship between the occurrence of beige adipocytes and M2-like macrophage recruitment. In order to investigate the role of CD206 M2-like macrophages in the induction of browning into the WAT, we extended our study to see the browning phenomenon by using CD206-ΔTDr and Tgfβ1 KO mice. Here, we showed that depletion of CD206 M2-like macrophages promotes the browning of WAT. We report that cold stimulation resulted in the generation of smaller adipocytes, upregulation of UCP1 and CD137, a marker for beige progenitors, in the WAT of CD206-ablated mice. Flow cytometry analysis further confirmed enhanced browning in the WAT. Since blocking of Tgfβ is known to promote browning of the WAT. Mechanically, we assume that enhanced browning into the WAT of CD206-DTR mice might be due to the deletion of Tgfβ1 from CD206-M2-like macrophages. Taken together, we concluded that CD206 M2-like macrophages induce the proliferation of beige progenitors in the WAT, which may serve as effective therapeutic tools for the prevention and treatment of obesity.
AMPK phosphorylation. Basal and AICAR-stimulated phosphorylation of AMPKFKO mice were not different between 8-27 weeks of age. Further, expression in epididymal, inguinal, and brown adipose tissues was reduced out mice (AMPKFKO) using the Cre-loxP system. AMPKα in Normal AICAR Tolerance and Glucose Metabolism

Phosphoregulation Profiles of Transcription Factors during Early Stage of Thermogenesis in Brown Fat

XIANG JING GAO, Shanghai, China

Brown adipose receives extensive attention for dissipating stored chemical energy in heat via nonshivering thermogenesis. However, whether and how the dynamics of key transcription factors (TFs) contributes to initial activation of thermogenesis remains unknown. Here, we employed the stat-of-the-art data-independent acquisition (DIA) mass spectrometry to explore the global and temporal phosphorylation profiles of signaling networks to elucidate mechanism responsible for the TF activation for thermogenesis gene transcription. The nucleus was isolated before and after stimulation for 5, 10, 20, 30, 40, 45, 50, 55, 60, 70 and 80 min with NE. Consequently, 401 transcription regulators bearing 1007 phosphosites were identified with high reproducibility across 12 time points. Firstly, the UCP1 transcriptional level was measured, which began at 30min, then rose until 70min in the peakness. The global phosphoproteome displayed dramatic changes early to 20-30min, which could be classified into two dynamic clusters, namely UCP1 pre-transcription phase and transcription phase. The former changed from 5min, and reached the extremum at 20-40min, which functioned before UCP1 action. Some well-characterized transcriptional regulators of UCP1 were found to be phosphorylated, such as PRDM16 and RIP140. Alternatively, other phosphorylation events of TFs such as Jun and ATF2 began from 30min, and maintained until 70min, almost synchronizing with UCP1 transcription. Intriguingly, we found THRAP3 posed multiple phosphosites but involving in different regulation partners. This might indicate that THRAP3 had distinct transcriptional regulation and functions upon thermogenesis. We, for the first time, uncovered temporal phosphoregulation profiles of TFs, which might be potentially required for initial activation of thermogenesis in brown fat. A new sight was provided to increase energy expenditure for treatment of obesity and other metabolic syndrome.

Adipose Tissue-Specific Knockout of AMPK alpha1alpha2 Results in Normal AICAR Tolerance and Glucose Metabolism

RAN HEC CHOI, ABISAIL MICOONAHAI, MACKENZIE B. JOHNSON, HO-JIN KOH, Columbia, SC

AMP-activated protein kinase (AMPK) is a member of Ser/Thr kinases that has been shown to regulate energy balance. Although recent studies have demonstrated the function of AMPK in adipose tissue using different fat-specific AMPK knockout mouse models, the results were somewhat inconsistent. Our previous study has shown that expression of AMPK activity in mouse adipose tissue, whereas high fat diet decreases its activity. For this study, we tested the hypothesis that AMPK in adipose tissue regulates whole body glucose metabolism. To determine the role of adipose tissue AMPK in vivo, we generated fat-specific AMPKα1/α2 knockout mice (AMPKFKO) using the Cre-loxP system. AMPKα1 and α2 protein expression in epididymal, inguinal, and brown adipose tissues was reduced by >80% in AMPKFKO mice compared to wild type littermates. Body weights of AMPKFKO mice were not different between 6-27 weeks of age. Furthermore, tissue weights (liver, kidney, muscle, heart and white and brown adipose tissue) were similar to wild type littermates and DEKA scan analysis revealed no differences in percentages of body fat and lean mass. Knockout of AMPKα1/α2 in adipose tissue abolished basal and AICAR-stimulated AMPK phosphorylation. Basal and AICAR-stimulated phosphorylation of Acetyl-CoA Carboxylase, a downstream of AMPK, was also reduced by 90% in AMPKFKO mice. Despite of the ablation of AICAR-stimulated AMPK phosphorylation, the blood glucose lowering effect of AICAR injection (i.p.) was normal in AMPKFKO mice. In addition, AMPKFKO displayed normal fasting blood glucose, glucose tolerance, and insulin tolerance, indicating normal whole body glucose metabolism. These data demonstrate that adipose tissue AMPK plays a minimum role in whole body glucose metabolism under normal condition.

Supported By: National Institutes of Health

Role of Adenyl Cyclase-Associated Protein 1 (CAP1) in Mediating Resistin Actions in Mouse Liver Cells

DIMITER AVTANSKI, ANABEL GARCIA, PRIYANTHAN THANGESWARAN, BEAT-RIZ CARDABALLO BORDUN, LEONID POEFTSKY, New York, NY

Resistin is a pro-inflammatory adipokine produced by the white adipose tissue (WAT) adipocytes and macrophages. Obesity results in chronic inflammation of the WAT, marked by an increase in resistance and other inflammatory cytokines, and by infiltrating leukocytes. Elevated resistin levels are believed to play a major role in the development of insulin resistance in the peripheral tissues. Adenyl cyclase-associated protein 1 (CAP1) was recently identified as a receptor for resistin. In the present study we aimed to investigate whether CAP1 mediates resistin actions which may affect insulin sensitivity in the liver. As a model we used BNL CL2 mouse liver cell line. Concentration- and time-dependent experiments demonstrated that resistin upregulated TNFα, SOCS3, IL-1α, and IL-6 mRNA expression maximally when used in concentration of 12.5 ng/ml for 6 hours. In order to determine the CAP1 involvement in mediating resistin actions in the liver, we transfected BNL CL2 cells with CAP1 siRNA and performed a real-time PCR array measuring the expression of 84 key genes involved in insulin-signaling, adipokine signaling, and inflammation. Results demonstrated that resistin upregulated mRNA expression of IL-6; this effect was ameliorated when CAP1 was downregulated. Knock-down of CAP1 facilitated mRNA expression of genes involved in insulin-signaling and adipokine signaling pathways, while it resulted in down-regulation of infiltrating leukocyte markers expression. Taken together these results indicate that CAP1 is a mediator of resistin actions in the liver.

Supported By: Gerald J. and Dorothy R. Friedman Foundation for Medical Research

Fibroblast Growth Factor-21 Maintains Glucose Homeostasis through Influencing the Expansion and Function of Subcutaneous Adipose Tissue

HUATING LI, LINLING QIAN, LIANG WU, Shanghai, China

Fibroblast growth factor 21 (FGF-21) has been extensively studied in recent years due to its multiple therapeutic benefits for a cluster of obesity-related cardiometabolic complications. However, an unsolved puzzle is that despite its pleiotropic metabolic benefits, FGF-21 is paradoxically elevated in obesity and diabetes in both animals and humans. Its pathophysiological relevance in response to excess energy intake remains poorly understood. Here we provide both clinical and animal evidences demonstrating that elevated endogenous FGF-21 in obesity serves as a defense mechanism against systemic insulin resistance. Serum FGF-21 levels were positively associated with subcutaneous fat area in subjects with insulin-sensitive overweight/obesity. Furthermore, FGF-21 knockout mice (FGF-21KO) showed much less subcutaneous adipose tissue (SAT) mass and were more insulin resistant when fed with high-fat diet. Replenishment of recombinant FGF-21 to a level equivalent to those occurring in diet-induced obesity restored SAT mass and reversed insulin resistance in FGF-21KO but not in adipose-specific FGF-21 knockout mice. Mice treatment of SAT from wild-type to FGF-21KO mice improved insulin sensitivity in the recipient mice. Mechanistically, circulating FGF-21 acts in an endocrine manner on subcutaneous fat to promote the healthy expansion. FGF-21 upregulates adiponectin in subcutaneous adipose tissue, accompanied with an increase of M2 macrophage polarization. This study raises the possibility that targeting subcutaneous fat manipulation of FGF-21 may represent a promising therapeutics to combat insulin resistance.

Supported By: National Natural Science Foundation of China (8122100808); National Natural Science Foundation of China (8166128016)
**Siah2 Expression in Adipocyte Progenitor Cells**

THANN DANG, GAIL E. KILROY, JESSICA L. TAYLOR, YOUNGMEI YU, ELIZABETH FLOYD, Baton Rouge, LA

Obesity-related insulin resistance is associated with adipose tissue inflammation and visceral adipose tissue expansion via adipocyte hypertrophy and impaired recruitment of new progenitor cells to undergo adipogenesis (hyperplasia). Deletion of the ubiquitin ligase Seven-in-absentia homolog 2 (Siah2) in obese mice significantly reduced adipose tissue inflammation and insulin resistance compared to obese wild type mice. However, larger adipocyte size accompanied this phenotype and subsequent experiments with adipose tissue stromal vascular fraction (SVF) cells showed adipogenesis required Siah2. In an earlier study, we found Siah2 affects adipogenesis by enhancing gene expression of the PPAR coactivator, Zfp423. ZFP423 is an early marker of preadipocyte determination that is activated during adipocyte lineage and links obesity to adipose tissue inflammation and insulin resistance.

*Supported by: National Institutes of Health (R01DK0398625)*

---

**Fat Shadows from DEXA for Documentation of Fat Distribution in Patients with Lipodystrophy**

RASIMCAN MERAL, BENJAMIN J. RYAN, JEFFREY F. HOROVITZ, ELIF A. ORAL, Ann Arbor, MI

Lipodystrophy (LD) syndromes are a heterogeneous group of disorders caused by atypical diabetes, associated with selective absence of fat with diabetes mostly depending on the clinical acumen of the physician. With niche therapies either approved or under investigation, development of objective diagnostic tools is urgently needed. Here we describe a new method using the built-in features of the enCore software v14.10 to render out non-fat tissues from Dual Energy X-ray Absorptiometry (DEXA) scans to derive a “fat-shadow” (Figure). We evaluated fat-shadows from 58 LD (60 F:M) patients and 91 non-LD patients (54 F:37 M). The LD, 3 had Generalized LD, 2 had Acquired Partial LD, and 53 had Familial Partial LD. Controls consisted of a mixed population of lean (12F:14M) or obese patients (39F:26M) with or without metabolic disease. There was substantial overlap in % body fat between the LD and non-LD groups (inter-quartile range: total, 22.2-38.9% vs. 33.6-45.9%; trunk, 27.0-46.8% vs. 39.1-50.2%; legs, 16.8-35.8% vs. 27.7-42.6%). However, fat-shadows obtained from patients with LD stood out due to the paucity of fat signal either in a generalized or regional manner compared to controls. Overall, fat-shadows provided sufficient qualitative information to infer clinical phenotype. We propose that these fat-shadows could be used for accurate documentation of fat distribution in LD.

*Figure.*

*Supported by: National Institutes of Health (R01DK088114, R21DK098776)*

Sophia Family, White Point Foundation of Turkey

---

**Comprehensive Analysis of the Characteristics and Differences in Adult and Newborn Brown Adipose Tissue**

CHUANHAI ZHANG, RUI LI, YAO SHENG, CUI YANG, XIAOYUN HE, WENTAO XU, KUNLUN HUANG, Beijing China

Brown adipose tissue (BAT) plays an important role in maintaining body temperature, treating obesity and diabetes. However, the amount and activity of BAT in adults (a-BAT) is very low, while the BAT in infant (i-BAT) is abundant and with strong activation. The a-BAT and i-BAT vary greatly in activation, but the characteristics and differences at the molecular level have not yet been fully revealed. We examined the changes in the mRNA expression of UCPI and thermogenic genes such as PRDM16, PGC1α, CPT1α and CPT1β in a-BAT and i-BAT of mouse. We found that, compared with i-BAT, T-cell, B-cell, and SCA-1 positive progenitor cells from mouse adipose tissues were analyzed for Siah2 expression. In parallel, in situ hybridization RNAscope of fat pads was employed to inspect Siah2 mRNA localization in adipose tissue. Since our evidence indicates Siah2 acts upstream of ZFP423, we predict Siah2 is expressed in adipocyte progenitor cells as well as immune cells in adipose tissue. This work will provide the groundwork to better understand how Siah2 controls commitment of progenitor cells to the adipocyte lineage and links obesity to adipose tissue inflammation and insulin resistance.

*Supported by: National Institutes of Health (R01DK0398625)*

---

**Early Changes in Glucose Homeostasis after Gastric Bypass Surgery in Patients with T2DM—Role of Adipose Tissue Mechanisms**

PETROS KATOGLIoANNiOs, GRETHE J. BQERMSA, FRASAO G. KAMBLE, MARIA J. PEREIRA, PER LUNDKVIST, ANDERS KARLSSON, SR., MAGNUS SUNDBOM, JAN W. ERIKSSON, Upsala, Sweden

Gastric bypass (GBP) surgery can effectively prevent or treat type 2 diabetes (T2D). Adipose tissue (AT) mechanisms may be important, but causality is not shown. We studied the relationship between early changes in whole-body and AT metabolism in obese T2D patients.

*Methods:* Eight T2D patients with BMI 30-45 (M:F 3/5, age 49 ± 10) underwent GBP following 4 week low calorie diet.

Assessments: OGTT, AT biopsies to measure gene expression in AT and in adipocytes, glucose uptake (GU), lipolysis and insulin action.

Results: At 4 and 24 weeks post-GBP, all subjects but one stopped diabetes medication. The Matsuda index increased compared to baseline, while HOMA-IR, fasting glucose, HbA1c and insulin levels decreased (p,< 0.01 for all). In adipocytes, basal, isoproterenol-stimulated or insulin-inhibited lipolysis rates and basal or insulin-stimulated GU did not change significantly. Mean adipocyte size was reduced, more at 4 than 24 weeks. At 4 week, expression of genes involved in fatty acid oxidation, CPT1b, cell proliferation, E2F1, and adiponectin were increased, whereas leptin was reduced (p,< 0.05 for all).

Conclusion: Glycemic control and insulin sensitivity clearly improved 4 weeks after GBP, but adipocyte insulin sensitivity in vitro did not improve despite a reduction in adipocyte size. Thus the mechanisms for rapid improvement of T2D after GBP may occur mainly in other tissues than adipose.

*Table.*

**Clinical and metabolic characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4-weeks post surgery</th>
<th>24-weeks post surgery</th>
<th>Adipocyte in-vitro data</th>
<th>Baseline</th>
<th>4-weeks post surgery</th>
<th>24-weeks post surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>37.3 ± 4</td>
<td>26.1 ± 1.3</td>
<td>26.1 ± 1.5</td>
<td>37.3 ± 4</td>
<td>37.3 ± 4</td>
<td>26.1 ± 1.3</td>
<td>26.1 ± 1.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>118.5 ± 22</td>
<td>197.4 ± 11.3</td>
<td>216.3 ± 11.4</td>
<td>240 ±4</td>
<td>216.3 ± 11.4</td>
<td>197.4 ± 11.3</td>
<td>240 ±4</td>
</tr>
<tr>
<td>Waist hip ratio (cm)</td>
<td>0.9 ± 0.0</td>
<td>0.9 ± 0.1</td>
<td>0.9 ± 0.1</td>
<td>0.9 ± 0.1</td>
<td>0.9 ± 0.1</td>
<td>0.9 ± 0.1</td>
<td>0.9 ± 0.1</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>42.4 ± 8</td>
<td>36.0 ± 8</td>
<td>30.7 ± 10</td>
<td>25 ± 10</td>
<td>36.0 ± 8</td>
<td>30.7 ± 10</td>
<td>25 ± 10</td>
</tr>
<tr>
<td>HbA1c (mmol/l)</td>
<td>48 ± 4</td>
<td>38 ± 5</td>
<td>33 ± 5</td>
<td>1000 µU/ml Insulin</td>
<td>38 ± 5</td>
<td>33 ± 5</td>
<td>1000 µU/ml Insulin</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>7.4 ± 1.8</td>
<td>5.8 ± 1.0</td>
<td>5.4 ± 1.0</td>
<td>Lipolysis (fM/cell/sec)</td>
<td>7.4 ± 1.8</td>
<td>5.8 ± 1.0</td>
<td>5.4 ± 1.0</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>6.3 ± 0.5</td>
<td>2.3 ± 1.3</td>
<td>1.2 ± 0.5</td>
<td>1.0 µU/ml Insulin</td>
<td>6.3 ± 0.5</td>
<td>2.3 ± 1.3</td>
<td>1.2 ± 0.5</td>
</tr>
<tr>
<td>Metabolite</td>
<td>1.08 ± 0.5</td>
<td>2.7 ± 0.5</td>
<td>1.7 ± 0.5</td>
<td>1.0 µU/ml Insulin</td>
<td>1.08 ± 0.5</td>
<td>2.7 ± 0.5</td>
<td>1.7 ± 0.5</td>
</tr>
<tr>
<td>Modified SRI</td>
<td>0.28 ± 0.0</td>
<td>0.30 ± 0.0</td>
<td>0.38 ± 0.0</td>
<td>0.45 µU/ml Insulin</td>
<td>0.28 ± 0.0</td>
<td>0.30 ± 0.0</td>
<td>0.38 ± 0.0</td>
</tr>
</tbody>
</table>

Data are means ± SD. Body fat % measured by bioimpedance. Different letters indicated significant differences between the visits; lower case letter: p<0.05; upper case letter: p<0.01. Iso, isoproterenol.

*1756-P*

---

**Moderated Poster Discussion**

---

**1757-P**

---

**Moderated Poster Discussion**

---

**1758-P**

---

**ADA-Supported Research**
both UCP1 and thermogenic genes were significantly decreased in a-BAT. Western blot data further confirmed the result. Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) also showed a clear distinction in a-BAT and i-BAT. Compared with a-BAT, the lipid droplet is less and mitochondrial density is higher in i-BAT. In addition, the characteristics and differences of a-BAT and i-BAT were comprehensively analyzed by mRNA, microRNA, LncRNA, circRNA, DNA methylation and proteome. Thousands of significantly changed IncRNAs and mRNAs as well as peptides were identified. Compared with i-BAT, we found hyper 383 and hyp 552 CMM related genes in a-BAT by differentially methylated region (DMR) analysis. What’s more, we found 1221 new circRNA in i-BAT and 1981 new circRNA in a-BAT and there were significant higher expression of circRNA in a-BAT compared with i-BAT. Furthermore, we constructed correlated expression networks circRNA-mRNA-LncRNA-methylation with bioinformatics methods. Co-expression analysis showed Inc-NONMMU0024827 and Inc-NONMMU0020705 expression is correlated with Fatty acid metabolism genes, including FASN and ACACA. Taken together, these results provide a better understanding of BAT function and development, and show a novel perspective roles of i-BAT or making a-BAT achieve the better activation and dynamic state just like i-BAT through the epigenetic modification.

Supported By: National Natural Science Foundation of China (81700684 to C.Z.)

1760-P

Adipose Tissue Transferin and Insulin Resistance
DON MCCLAIN, NEERAJ K. SHARMA, FELIPE LORENZO, SHALINI JAIN, CLAUS D. LANGEfeld, MARY E. COMEAU, ILPIKA SALAYE, SWAPAN K. DAS, Wiston-Salem, NC

Iron is an important micronutrient involved in several metabolic processes, and excessive iron is a risk factor for insulin resistance (IR) and diabetes. To define the genetic regulation of iron metabolism and its role in IR, we used gene expression, genotype, and insulin sensitivity data from an African American cohort (AAGMEx, N=256). Among the genes in a manually curated list of 62 transcripts representing iron homeostasis genes, expression of 32 in adipose tissue showed significant correlation with S, p<0.01. The expression levels of transferrin (TF, β= 0.23, p=7.84 x 10^-6) and ferritin heavy chain (FHT, β=1.2, p=7.5 x 10^-10) in adipose tissue were the most positively and negatively associated with S, respectively. Observations were replicated in independent adipose tissue data sets from individuals of European ancestry (ARRCA, N=99; METSIM, N=720). Among these S-associated transcripts, the strongest cis-regulatory genetic variant (rs-eSNP) was for TF rs6785596, β= -0.962, p=7.94 x 10^-10) in adipose, but not in muscle or liver. To identify the role of TF in adipocytes, we downregulated its expression in a human adipocyte cell model (SGBS). Gene specific siRNA knockdown of TF caused differential expression (log2FC +/-0.4, probability>70%) of 465 genes, involved in mitochondrial function (CPT1B, UCP2), glucose transport (GLUT4), Wnt-pathway insulin sensitivity (SRPR, SRPR1), chemokine cytokine-cell-cell interaction (CXCL1, CXCL12, ICAM1), and genes with possible roles in obesity (CE51, RARRES2). Knockdown of TF mRNA in differentiated SGBS cells impaired mitochondrial respiration (40%10% reduction of maximal oxygen consumption rate) and caused a 34% reduction in maximal insulin-stimulated glucose uptake (p<0.05).

In summary, genetic regulation of transferin expression in adipose tissue plays a novel role in regulating insulin sensitivity.

Supported By: National Institutes of Health (U.S. Department of Veterans Affairs ADA-Supported Research

1761-P

DBC1, Deleted in Breast Cancer 1, Is a Nuclear STAT5A-Interacting Protein in Adipocytes, but Its Primary Effects on GLUT4 Gene Expression and Lipolysis Are STAT5 Independent
ASHLEY ABLE, ALLISON J. RICHARD, JACQUELINE M. STEPHENS, Baton Rouge, LA

STAT5A (signal transducer and activator of transcription 5A) is a transcription factor that plays a role in adipocyte development and function. Although the role of STAT5A in fat cell development is well characterized, its specific roles in mature fat cells are still largely unknown. Moreover, the potential role of STAT5A in metabolic diseases, in particular type 2 diabetes, remains unclear. To further understand the function of STAT5A in adipocytes, we employed a non-biased co-immunoprecipitation and mass-spectrometry-based approach to identify novel STAT5A-interacting proteins. One of the proteins we identified was DBC1 (deleted in breast cancer 1; also known as CCAR2). DBC1 is typically localized in the nucleus and has been primarily studied in tumor cells. However, the functions of DBC1 in adipocytes are relatively unknown. Using mouse fat cells, we confirmed that there is a physical association between endogenous STAT5A and DBC1 proteins under physiological conditions in the nucleus that is not dependent upon STAT5 expression. Knockdown of DBC1 in 3T3-L1 adipocytes using siRNA did not affect the expression of several STAT5A target genes including socs3, cish, bc-1, isoc2, and igf-1. However, we did observe increased levels glyceral and free fatty acids released from adipocytes with reduced DBC1 following TNF (tumor necrosis factor) stimulation. Although loss of STAT5A did not alter STAT5A transcriptional activity for the genes examined, it appears to modulate TNF-mediated lipolysis in a STAT5-independent manner. In addition, DBC1 knockdown increased GLUT4 expression in murine fat cells but did not have a profound effect on TNF-mediated changes in gene expression. On-going studies are being performed to elucidate the function of the DBC1/STAT5A interaction and to clarify the impact of DBC1 on lipolysis in adipocytes.

Supported By: National Institutes of Health (R01DK052988)

1762-P

Constitutively Active Grp1 Promotes Basal Glucose Transport into White Adipose and Enhances Insulin Sensitivity in High-Fat Fed Mice
KYLE D. COPPS, JIAN LI, BOSTON, MA

Insulin-stimulated phosphorylation of Grp1 (general receptor for phoshoinsitides; a.k.a Cyth3, cytoserin) in cultured adipocytes is known to promote recycling of insulin-regulated glucose transporter (Glut4)-containing vesicles from the endosome to plasma membrane, and to enhance glucose uptake thereafter. We found that Cre-dependent expression of a constitutively active form of Grp1 (caGrp1) specifically increased basal glucose uptake into WAT of young Chow-fed mice, without altering Akt phosphorylation or insulin-stimulated uptake. Although early growth and glucose homeostasis in Chow-fed caGrp1 mice were normal, caGrp1 mice fed a high fat diet (HFD) became markedly less adipose, and showed improved glucose tolerance and insulin sensitivity vs. Cre-negative controls. Fasting insulinemia in HFD-fed caGrp1 mice was lower, whereas circulating adiponectin was higher, and FGF-21 and leptin were unchanged. Hepatic lipid disposition in HFD-fed caGrp1 mice was comparable to that in controls, though circulating and liver free fatty acids were slightly lower. However, epigonal WAT from caGrp1 mice showed markedly reduced staining for inflammatory marker CD68, and adipocyte size was also significantly greater. Collectively, these features distinguish caGrp1 mice from those with adipose-specific over-expression of Glu4 described by others, but remain compatible with an adipose-specific basis of improved systemic insulin sensitivity. Given recently improved understanding of the structural/functional changes induced in Grp1 via Akt phosphorylation, drug-based activation of Grp1 in WAT might prove an attractive route by which to favorably alter systemic insulin sensitivity and glycemia.

Supported By: American Heart Association

FSP27-Rab18-Vimentin Regulates Lipid Droplet Trafficking and Insulin Signaling in Adipocytes
VISHWAJEET PURI, SAYANI BANERJEE, SUKANTA JASH, ATHENS, OH

FSP27-Rab18-Vimentin Regulates Lipid Droplet Trafficking and Insulin Signaling in Adipocytes

Supported By: National Institutes of Health (R01DK052988)

1763-P

Constitutively Active Grp1 Promotes Basal Glucose Transport into White Adipose and Enhances Insulin Sensitivity in High-Fat Fed Mice
KYLE D. COPPS, JIAN LI, BOSTON, MA

Insulin-stimulated phosphorylation of Grp1 (general receptor for phoshoinsitides; a.k.a Cyth3, cytoserin) in cultured adipocytes is known to promote recycling of insulin-regulated glucose transporter (Glut4)-containing vesicles from the endosome to plasma membrane, and to enhance glucose uptake thereafter. We found that Cre-dependent expression of a constitutively active form of Grp1 (caGrp1) specifically increased basal glucose uptake into WAT of young Chow-fed mice, without altering Akt phosphorylation or insulin-stimulated uptake. Although early growth and glucose homeostasis in Chow-fed caGrp1 mice were normal, caGrp1 mice fed a high fat diet (HFD) became markedly less adipose, and showed improved glucose tolerance and insulin sensitivity vs. Cre-negative controls. Fasting insulinemia in HFD-fed caGrp1 mice was lower, whereas circulating adiponectin was higher, and FGF-21 and leptin were unchanged. Hepatic lipid disposition in HFD-fed caGrp1 mice was comparable to that in controls, though circulat-
**Adipocyte Gamma-Secretase Inhibition May Alter IL-6 Expression and Trafficking**

DAVID SPARLING, NILE MCCULLOUGH, Oklahoma City, OK

Adipocyte-mediated inflammatory signaling has been proposed to alter adipose physiology in obesity. Activation of adipocytes can increase secretion of inflammatory cytokines such as IL-6. IL-6 secretion is regulated through changes in expression of both IL-6 itself, as well as its specific SNARE trafficking machinery. Recent data suggests that the γ-secretase enzyme complex is involved in both adipose insulin sensitivity and immune system regulation. We therefore hypothesized that adipocyte IL-6 secretion could be altered by γ-secretase inhibition. To explore this hypothesis, 3T3-L1 adipocytes were stimulated with lipopolysaccharide (LPS) in the absence or presence of a γ-secretase inhibitor. Changes in gene expression of inflammatory cytokines and SNARE complex components, including IL-6, MCP1, Stx6, Vtnb, SCARNS, VAMP3, Stx4, and SNAP23 were examined by qRT-PCR, and immunofluorescence (IF) was used to determine adipocyte IL-6 expression and localization. IL-6 secretion was analyzed by ELISA. Transcription of IL-6 and several of the SNARE complex proteins were not significantly affected by γ-secretase inhibition. However, total cellular IL-6 increased by LPS stimulation by IF, which could be blocked by pre-treatment with a γ-secretase inhibitor. IL-6-associated SNARE component Vtnb mRNA levels were specifically affected by overnight γ-secretase inhibition. LPS stimulation increased Vtnb1b transcription 3-fold, which was completely blocked by γ-secretase inhibition (p<0.01, n=6 per condition). Increasing amounts of LPS (range 0 to 10 ng/mL) for 6 hours led to an expected increase in IL-6 secretion, which was significantly blocked by overnight pre-treatment with a γ-secretase inhibitor. LPS-stimulated IL-6 secretion could also be decreased by short-term (20 minute) γ-secretase blockade. Taken together, this data suggests that the γ-secretase enzyme complex may be involved in a variety of signaling cascades controlling both the production and secretion of IL-6 in adipocytes.

Supported By: National Institute of Diabetes and Digestive and Kidney Diseases (DK068117-01)

**Silencing Mediator of Retinoid and Thyroid Hormone Receptors (SMRT)—A Link between Adipocytes, Inflammation, and Glucose Intolerance**

JONATHAN KAHN, ANNA A. GODDI, RONALD N. COHEN, Chicago, IL

Silencing Mediator of Retinoid and Thyroid Hormone Receptors (SMRT) is a nuclear corepressor, which regulates the transcriptional activity of metabolically essential transcription factors. While SMRT has been shown to modulate adipocyte function, in vivo experiments utilizing knock-out (KO) models have led to conflicting results. To more rigorously define the role of SMRT in the adipocyte, we generated adipocyte-specific SMRT KO (adSMRT KO) mice by crossing adiponectin-Cre mice with floxed SMRT mice on a C57/BL6 background. When adSMRT KO mice are challenged with a 45% high-fat diet, we observe 20% increase in glucose intolerance (p=0.006) compared to wild type (WT) counterparts. Additionally, RNA-Seq data of adipose tissue from these mice indicate a dramatic up-regulation of inflammatory gene expression. To further characterize the pro-inflammatory phenotype, we utilized flow cytometry to identify infiltration of specific populations of adipose tissue inflammatory cells. We found that overall macrophage infiltration in the adipose tissue of KO mice increased two-fold (p=0.028), with anti-inflammatory M2 macrophages infiltrating in significantly lower proportions (p=0.017), indicating a higher ratio of M1:M2 cells in the KO mice compared to WT. In contrast, body weight and total fat mass were not altered. These data suggest a role for SMRT in the cross-talk between adipocytes and pro-inflammatory macrophages for the regulation of systemic glucose tolerance, distinct from the development of obesity. SMRT therefore integrates metabolic and inflammatory signals to maintain physiological homeostasis.

Supported By: American Diabetes Association (17-BS-033 to R.N.C.)
A Positive Allosteric Modulator Enhances the Ability of Beta Cell M3 Muscarinic Receptors to Simulate Insulin Secretion In Vitro and In Vivo
LU ZHU, JÜRGEN WESS, Bethesda, MD

Several studies have shown that activation of M3 muscarinic acetylcholine (AcH) receptors (M3Rs) expressed by pancreatic beta-cells leads to striking increases in glucose-stimulated insulin release. As a result, we hypothesized that agents that can promote signaling through beta cell M3Rs might become useful in the treatment of type 2 diabetes. The M3R is a prototypic A GPCR that is selectively coupled to G proteins of the Gq family. At present, selective M3R agonists that bind to the orthosteric ACh binding site are not available. However, the lab of Craig Lindsay (Bridges et al., 2010) recently described a compound (VU019498) that binds to an allosteric site on the M3R, thus enhancing ACh-induced signaling through M3Rs. In this study, we tested the ability of this positive allosteric modulator (PAM) to stimulate insulin release in vitro and in vivo. The use of PAMs has the great advantage that it respects the spatio-temporal control of receptor activation, i.e., the PAM is only active upon receptor occupation by an endogenous orthosteric agonist. Studies with cultured MIN6-cells showed that VU019498 enhanced ACh-induced insulin secretion in an M3R-dependent fashion. In vivo studies demonstrated that PAM treatment of WT mice caused a significant increase in plasma insulin levels, accompanied by a striking improvement in glucose tolerance. These VU019498 effects were mediated by beta-cell M3Rs since they were absent in mutant mice selectively lacking M3Rs in beta-cells. In future studies, we will use mouse models of diabetes to examine whether this M3R-PAM is endowed with anti-diabetic activity. This approach may lead to the development of a novel generation of anti-diabetic drugs.

Identification of Mitochondrial Pyruvate Carrier Modulator to Treat Diabetes
KYLE S. MCCOOMMS, WESLEY T. HODGES, YANA CHEN, KARI CHAMBERS, BRIAN N. FICK, ST. LOUIS, MO

Recent work conducted in knockout mouse models or using small molecule modulators of the mitochondrial pyruvate carrier (MPC) have suggested that targeting this protein complex may have efficacy for treating diabetes as insulin sensitizers. To begin to identify other small molecules that interact with the MPC and could potentially be new therapeutic leads, we used a BRET-based MPC reporter assay (reporter sensitive to pyruvate; RESPYR) system that responds to molecules that interact with the pyruvate binding site of the complex. Screening of a 1800 molecule chemical library generated a number of hits for compounds that activated RESPYR activity. Some of these had confirmed previous reports of MPC interacting drugs, including the insulin-sensitizing thiazolidinediones, pioglitazone and rosiglitazone. Another hit in this screen was Zaprinast, an inhibitor of phosphodiesterase 5 (PDE5). Zaprinast affected RESPYR activity in a dose-dependent manner and at high mM concentrations. Zaprinast also potently inhibited pyruvate-mediated respiration in isolated WT, but not MPC-deficient mitochondria, demonstrating a direct mitochondrial effect and MPC-dependence for this inhibition of pyruvate metabolism. Analyses using other PDE5 inhibitors (Sildenafil, Tadalafil, and Vardenafil) showed no effect on RESPYR activity or mitochondrial respiration. Consistent with the concept that hepatic gluconeogenesis from pyruvate requires mitochondrial pyruvate import, Zaprinast reduced production of glucose from pyruvate in WT, but not MPC-deficient hepatocytes in vitro. Studies are ongoing to determine whether Zaprinast treatment will lower blood glucose in vivo. In conclusion, these data demonstrate the feasibility of screening for novel MPC interacting compounds to identify novel therapeutics for treating diabetes and other metabolic diseases and also suggests that the orphan drug Zaprinast may be a novel anti-diabetic agent.

Absence of Changes in Galectin-3 with Insulin Sensitization and Anti-Inflammation
PARESH DANDONA, HUSAM GHANIM, MANASI S. SHAH, KELLY GREEN, ANTOINE MAKDISSI, AJAY CHAUDHURI, WILLIAMSVILLE, NY, BUFFALO, NY

Galectin-3 (gal-3) has recently been shown to mediate insulin resistance in mice. Its deletion leads to insulin sensitization while its excess is associated with insulin resistance. We, thus, undertook an investigation into its role in the reversal of insulin resistance in three human models of insulin sensitization: 1) 6 months following bariatric surgery (RYGB) and weight loss in patients with morbid obesity; there was a reduction in BMI from 52.1±4.8 to 40.4±4.0 kg/m² (p<0.001) and HOMA-IR fell from 7.1±1.1 to 2.1±0.3 (p<0.001; 2) 12 weeks of pioglitazone (45mg/day) treatment in obese patients with type 2 diabetes, where HOMA-IR fell from 3.5±0.7 to 2.1±0.4; and 3) following 6 months of testosterone replacement in obese patients with type 2 diabetes and hypogonadism, where HOMA-IR fell from 4.2±0.9 to 2.7±0.4. Gal-3 levels at baseline were 7.6±1.1, 5.7±0.9 and 4.4±0.7ng/ml, respectively. In all three models, there was no significant change plasma concentrations of gal-3 (0.8±1.2, 5.9±0.9 and 5.8±0.9ng/ml, respectively) following interventions. There was no change in type 2 diabetes. Many G protein-coupled receptors (GPCRs) are expressed in insulin sensitive organs and thus have emerged as potential targets for novel antidiabetic drugs. P2Y purinergic receptors are a class of GPCRs activated by nucleotides and nucleotide sugars. The purinergic P2Y receptor (P2Y1R) is activated by uridine 5'-diphosphate. The potential role of P2Y1R in adipose tissue and skeletal muscle with respect to maintaining whole body glucose homeostasis remains unexplored. To address this issue, we used Cre/loxP technology to generate mice that lack P2Y1R selectively in adipose tissue (AT-Y6-KO) or skeletal muscle (SK-Y6-KO). Interestingly, AT-Y6-KO mice consuming a high fat diet gained less weight, while SK-Y6-KO mice gained more weight than the corresponding control mice. Body composition revealed that the difference in body weight was due to loss or gain in fat mass in AT-Y6-KO and SK-Y6-KO mice, respectively. Improved vs. impaired glucose tolerance and insulin sensitivity was observed in AT-Y6-KO and SK-Y6-KO mice, respectively. Moreover, fasting blood glucose and fed plasma insulin levels were decreased in AT-Y6-KO mice. SK-Y6-KO mice showed elevated blood glucose and plasma insulin levels under both fasting and fed conditions. Detailed mechanistic studies are required for understanding the role of P2Y1R in metabolic tissues and to alter its function for therapeutic purposes.
Regulation of Insulin Sensitivity by Phosphorus

YI LIN, LINDSEY BERGER, ZHONGJIE SUN, Oklahoma City, OK

Diabetic phosphorus excess as a result of the ever growing consumption of highly processed foods has been associated with developments of ageing related diseases such as diabetes and obesity in the general human population. Insulin resistance is the main feature of aged human population especially in patients with type 2 diabetes and some people with obesity. Thus, the study of a low phosphorus diet on glucose homeostasis such as insulin resistance and glucose tolerance is of great interest. Here, we investigated glucose homeostasis in male and female 129Sv mice fed with low phosphorus diet (0.2% of Pi) vs. control diet (0.4% of Pi). Interestingly, the fasting basal glucose level dropped significantly in male mice after being fed with low Pi diet for 4 weeks. In addition, low Pi diet significantly enhanced insulin sensitivity in both male and female mice. Furthermore, low Pi diet lowered serum Pi levels in mice of both genders without interrupting the growing pattern of body weights during the 10-week feeding period. Examination of proteins with Western Blot revealed that low Pi diet significantly enhanced insulin receptor β IRβ levels in skeletal muscles. In vitro experiments indicated that low Pi enhanced and high Pi inhibited insulin signals such as tyrosine phosphorylation of IRβ (Tyr1150/1151) and serine phosphorylation of Akt (Ser473) in primary culture of human skeletal muscle cells (HSKMCs). In addition, low Pi increased high Pi decreased insulin-induced glucose uptake in HSKMCs. Therefore, these data indicate that low Pi diet regulates glucose homeostasis, partly via enhancing insulin sensitivity through upregulating insulin signal and insulin-induced glucose uptake in skeletal muscles.

Supported By: National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases (RO1093403)

Differential Impacts of Insulin Analog Lispro and Glulisine on Glucose and Lipid Homeostasis during Hyperinsulinemic Euglycemic Clamp in Streptozotocin-Induced Diabetic Rats

FRANÇOIS BRIAND, EMMANUEL BROUSSEAU, RÉMY BURCELIN, THIERRY SUL-RISE, Lábège, France, Toulouse, France

In addition to their benefits on glycaemia, the specific actions of insulins on glucose and lipid metabolism should be depicted. Here we analyzed the effects of Lispro (LIS) and Glulisine (GLU) insulin-analogs in diabetic rats. Diabetes was induced in Wistar male rats following an i.v. injection of streptozotocin (STZ, 60mg/kg). Conscious rats underwent a 2-hour hyperinsulinemic (LIS or GLU at 0.8U/kg/h) euglycemic clamp with a constant infusion of 3H-glucose (4µCi/kg/min), with n=8 rats per each group. Glycemia was measured continuously to adjust glucose infusion rate (GIR) to maintain euglycemia during the LIS or GLU perfusion. Blood, muscle and liver samples were collected for biochemical and radioactivity analysis. Compared to LIS, mean GIR was 51% higher in LIS treated rats (LIS: 14.4 +/- 3.2 mg/kg/min, GLU: 6.4 +/- 1.6 mg/kg/min, p<0.01). Whole body glycogen, glycerogen, as well as liver and muscle glycogen synthesis rates remain similar between groups. Compared with LIS, rats treated with GLU showed a better reduction in plasma free fatty acids and glycerol levels during the clamp experiment, with a 50% and 130% lower plasma free fatty acids and glycerol area under the curve (p<0.05 and p<0.01 vs. LIS, respectively). β-Hydrogen incorporation in muscle and liver lipid stores was not different, indicating that lipolysis rather than lipogenesis was differentially impacted.

In conclusion, hyperinsulinemic euglycemic clamps in STZ rats enabled to detect a strong inhibition of hepatic glucose production by LIS, while GLU better suppresses lipolysis. Our experimental setting should help to differentiate other insulin analogs and dissect their mechanisms of action.

An Oral Glucose Load Decreases Post-Prandial Microparticles in Obese Adults With and Without Prediabetes

NATALIE EICHNER, NICOLE M. GILBERTSON, LUCA MUSANTE, SABRINA LA SALVIA, EUGENE BARRETT, ARTHUR WEITLMAN, UTA ERDBRUEGGER, STEVEN K. MALIN, Charlotteville, VA

Microparticles (MPs) are a novel mediator and/or biomarker of cardiovascular disease (CVD) and type 2 diabetes. A high fat meal can facilitate MP release in relation to CVD risk, but the effects of carbohydrates are unknown. This is clinically relevant as low-fat diets are advised for glycemic control. We tested the hypothesis that a 75g oral glucose tolerance test (OGTT) would promote changes in MPs linked to CVD risk. Twenty-five obese adults (Age: 52.4±3.2y, BMI: 32.5±1.2kg/m²) were screened for prediabetes using ADA criteria (75g OGTT and/or HbA1c). Eight were normal glucose tolerant (NGT) and 17 had prediabetes (PD). Blood composition (bioelectrical impedance) was measured and arterial stiffness (augmentation index; AI) insulin and glucose were collected at 0 and 2 hour of the OGTT to assess CVD risk. Annexin V+ (AV+) and Annexin V- (AV-) total MPs and platelet MPs (CD31+/CD41+; CD41+) were also collected at these times and analyzed from fresh plasma via imaging flow cytometry. There were no statistical differences in age, BMI, or body fat (all P>0.2) between NGT and PD, although fasting and 2 hour glucose as well as insulin were higher in PD vs. NGT (P<0.03). Glucose and insulin increased during the OGTT (both P<0.005), while arterial stiffness at 2 hour decreased by 6.9% (P=0.06). Fasting MPs were not different between groups. Total MPs, AV- CD41+ and AV- CD31+/CD41+ MPs decreased after the OGTT (P≤0.04), while AV+ CD41+ (P<0.08) and AV+ CD31+ (P<0.10) trended. Attenuated OGTT insulin responses were related to lower post-prandial platelet AV- CD31+/CD41+ (r=-0.46, P=0.06) and AV- CD41+ (r=-0.45, P=0.06) MPs, while arterial stiffness was associated with reduced total MPs (r=-0.49, P=0.03) and AV-CD41+ (r=-0.52, P=0.02). An oral glucose load lowered post-prandial total and platelet MPs in obese adults with NGT and PD. Further work is required to examine MP content in order to gain mechanistic insight for optimizing type 2 diabetes management.

Supported By: University of Virginia Curry School of Education

Mechanism Mediated by S6 Kinase Resulting in both Sufficient Glucose Metabolism Improvement and Insufficient Weight Loss by Glucose Excretion against Fat Load

TAKAKI KIKUCHI, AKIFUMI KUSHIHAMA, MIDORI FUJISHIRO, HIDETUKI SAKODA, TOMOICHIRO ASANO, YASUHIKO IWAMOTO, Tokyo, Japan, Miyazaki, Japan, Hiroshima, Japan

SGLT2 inhibitors have succeeded in improving prognosis in addition to blood glucose control and weight loss in T2D patients, but the reason is unclear. Systemic metabolic changes when improvement by glucose excretion is not sufficiently elucidated. Here, metabolic respiration balance and insulin signal change were analyzed when the high fat diet-induced insulin resistance was improved with the SGLT2 inhibitor tofogliflozin. 8-week-old male C57/B16 mice were divided into 3 groups; normal feed group (N group), 60% high fat (HF) feed group and 0% high fat feed group. After 8 weeks of feeding, the body weight increased by 30% in the HF group compared to the N group and by 16% in the Tofo. Both IPITT and IFITT were improved in the Tofo compared with HF group. In the calorimetric analysis, the heat production increased, the respiratory exchange ratio (RER) decreased, and the RER diurnal variation disappeared in the HF group, while the Tofo reduced the energy consumption to the same level as the N group while maintaining the RER equivalent to the HF group. UCP1 in brown fat was elevated in the HF group and improved in the Tofo. Phosphorylation of the basal S6K was enhanced in the HF group and disappeared in the Tofo, while after insulin administration, pAkt and resulting pS6K were accelerated in the Tofo.

In conclusion, urinary glucose excretion against high fat load is resulting in improvement of IRS-1 degradation by basal S6Kinase promotes insulin Akt activation. Lipid synthesis is enhanced by insulin while energy expenditure is normalized. Inhibited fat burning compensation leaves weight gain, but since insulin signal has been improved enough, glucose metabolism is improved adequately. This suppression of catabolism might be involved in the improved prognosis by administration of SGLT2 inhibitors.
Impact of Blood Sugar Control on Metabolites and Carbohydrate Metabolism in Type 1 Diabetes

WILLEM KUNTREBRE, SOPHIE E. JANES, MICHAEL W. YANG, DENISE L. FAUST-MANN, CHARLESTON, SC; BOSTON, MA

In type 1 diabetes (T1D), long-term blood sugar control measured by HbA1c can vary over a wide range. Although metabolites are commonly studied in type 2 diabetes (T2D) as they relate to HbA1c, similar studies in T1D are few. Since the underlying etiologies of T1D and T2D are different, we explored the overall pathways of metabolism in T1D subjects with tight vs. poor blood sugar control. T1D subjects (n=50) were divided into two groups (n=25 each) based on low vs. high HbA1c (Screen 1, low: mean 6.7 ± 0.1%; high: mean 8.7 ± 0.3%). Serum samples were analyzed on a metabolomic GC/HPLC/MS platform and analyzed for differences in biochemicals between the groups. The screen was repeated with a second group of 50 patients for verification (Screen 2, mean 6.3 ± 0.1%; mean 8.0 ± 0.2%) and then both screens combined. For each detected biochemical, average scaled intensity was determined and statistical significance of differences was calculated using a two-tailed, unpaired Student’s T test (p-values) and False Discovery Rate (q-values). The platform distinguished 690 components in Screen 1 and 623 biochemicals in Screen 2. In Screen 1, two biochemicals, including glucose, showed significant differences (p<0.05) for both p and q values. In Screen 2, none of the biochemicals reached threshold. When the screens were combined (100 samples), 10 biochemicals were significant for both p and q. Three components (glucose, mannose and 1,5-AG) were correlated to blood sugar control and thus expected in a high and low HbA1c analysis. Significant biochemicals commonly found in T2D and related to blood sugar control were not significant in T1D for both p and q in the screens. We conclude that few metabolites are correlated in T1D with tight vs. poor blood sugar control compared to T2D. Unlike T2D, metabolites related to intracellular sugar utilization, the Krebs cycle and purine synthesis are unrelated to blood sugar control in T1D cohorts.

Actions of Apolipoprotein A-IV on Insulin-Independent Glucose Control and Activation of Akt in Mouse Liver

JING HE, JING ZHAO, ZIYU YANG, JIANBO ZHANG, SHUQIANG WEI, SHENGBIN LI, XIAOMING U, XIN Can

Insulin resistance is a risk factor for type 2 diabetes, fatty liver and metabolic syndrome. We reported previously that apolipoprotein A-IV (ApoA4) increased insulin secretion, insulin sensitivity and improved glucose uptake in adipocytes by PI3K-Akt pathways. Whether insulin sensitivity is improved by ApoA4 in mouse liver remains unclear. Here we used mice as well as hepatocytes to investigate the action of ApoA4 on glucose control and hepatic Akt activation. Liver tissues were from lean mice 2 h after a single ip injection of recombinant mouse ApoA4 (n = 5 per group) and tissue lysates were separated by Western blotting with anti-p-Akt antibody. Primary mouse hepatocytes were cultured for glucose uptake experiment and p-Akt analysis after ApoA4 stimulation. Approach to block insulin secretion transiently and insulin-resistant DIO mice (db/db-HFD) and lean mice by propranolol and epinephrine was used by co-administration with glucose after a single ip injection of ApoA4 prior to being sacrificed for the liver. Treatment of the mice with ApoA4 for 2 h increased Akt phosphorylation from liver in dose-dependent manner, direct action of ApoA4 on Akt activation in primary mouse hepatocytes too indicates this effect was insulin independent. ApoA4 treatment also increased [3H]-2-deoxyglucose uptake by primary mouse hepatocytes. The contributions of ApoA4 on insulin-independent glucose disposal was verified with insulin blocking. ApoA4 to an equal extent of direct insulin-independent and insulin-dependent, enhanced blood glucose clearance in both insulin-resistant DIO mice and lean mice. With the glucose challenge, ApoA4 treatment resulted in an increase in Akt phosphorylation in liver, heart and brown adipose tissue in insulin-dependent in lean mice, but which was in insulin-independent only in liver in DIO mice. Data imply ApoA4 as a novel antiobisdiabetic drug to treatments of diabetic diseases.

Supported By: Key Scientific and Technological Fund of Shandong Province, China (2016ZD02); Key Scientific Research Fund (No. X.L.)
INSULIN ACTION—SIGNAL TRANSDUCTION, INSULIN, AND OTHER HORMONES

1780-P
Generation of a Novel Gene Therapy Vector Encoding Beta-Cell-Specific Insulin for Diabetes Treatment
ELIF O. SAHIN, FULTA ERENDOZ, MUSTAFA KEMAL BALCI, SALIH SANLISOGLU, Antalya, Turkey
Insulin injection is the main treatment modality especially for patients with type 1 diabetes. Despite the development of several insulin analogs, recent meta-analysis indicated that rapid and long acting insulin analogs provide little benefit compared to conventional insulins regarding to glycemic control. Therefore, gene therapy methods are investigated to develop a novel treatment approach to reconstitute a natural endogenous insulin expression profile in diabetic patients. For this purpose, Multisite Gateway Technology was employed to generate a transfer vector carrying lentiviral backbone with minimal insulin promoter hooked up to proinsulin gene sequence. Following construction of the transfer plasmid by restriction enzyme digestion and DNA sequence analysis, high-titer LentiINS vectors at a concentration of 10^8 TU/ml were successfully produced by CaPO4 cotransfection of 293T cells with packaging and transfer plasmids. While transduction of NIT1 mouse pancreatic beta cell lines produced fold increase in insulin gene expression compared to controls, no insulin expression was detected in 293T kidney cell line. These results indicate that we successfully constructed an HIV-based lentiviral gene therapy vector being capable of beta-cell-specific insulin gene expression and secretion (TUBITAK 211S820).

Supported By: Scientific and Technical Research Council of Turkey (TÜBİTAK 211 S820)

1781-P
Aquaporins-1 and -3 Play Novel, Distinct Roles in Normal Balanced Insulin Signaling
XIANGGAO WU, KEVIN JON WILLIAMS, Philadelphia, PA
Patients with overnutrition, obesity, the atherometabolic syndrome, and type 2 diabetes exhibit imbalanced insulin action, also called pathway-selective insulin resistance. To control glyceremia, they require hypoinsulinemia that then overdrives ERK and hepatic de-novo lipogenesis (DNL). We discovered an oxidative transport chain that is required for balanced insulin action (Atherosclerosis 2016;247:225). The chain, abbreviated "NSAPP," begins when insulin stimulates NOX4 to generate O2⋅−/NOX4 hands O2− to O2$ for conversion into H2O2. Aquaporins (AQPs) channel this H2O2, to inactivate PTEN. Disruption of any component, from NOX4 up to PTEN, leaves PTEN persistently active, thereby producing the same deadly pattern of imbalanced insulin action.

We now sought to identify which aquaporins mediate balanced insulin signaling in hepatocytes. Four AQP s had been reported to act as pores for H2O2: AQP1, 3, 8, and 9. We found that global inhibition of all APQs with low-dose AgNO3 recapitulated the clinical pattern of imbalanced insulin signaling, i.e., full two-site phosphorylation of ERK (pT202/Y204-ERK) and pT308-AKT, with only weak phosphorylation at Ser473; robust phosphorylation of AKT targets leading to DNL; but impaired AKT-mediated phosphorylation of FoxO1 (needed to suppress hepatic gluconeogenesis). Our knockdown of AQP3 recapitulated this pattern of imbalanced insulin signaling. Knockdown of AQP1 produced the mirror-image: strongly inhibited pT202/Y204-ERK and pT308-AKT, but intact pS473-AKT. Knockdowns of AQP6 or AQP9 did not affect insulin signaling to either site on ERK or AKT. Importantly, immunoprecipitation of AQP3 brought down PTEN, a previously unknown partner of any aquaporin.

Thus, AQP3 participates in the NSAPP oxidative transport chain. AQP1 plays an unrelated role, perhaps as a scaffold. Our findings will facilitate unraveling the molecular basis for NSAPP dysfunction in overnutrition and hence imbalanced insulin action.

Supported By: American Diabetes Association (1-13-BS-209 to K.J.W.)

1782-P
Preserved Beta-Cell Function during Acute DKA in Ketosis-Prone Diabetes
PARAS B. MEHTA, SURYA N. MULUKUTLA, JEAN W. HSU, KELLY R. KEENE, NAULINI RAM, ASHOK BALASUBRAMANIAM, Houston, TX

Introduction: Ketosis prone diabetes (KPD) comprises heterogeneous syndromes characterized by presentation with DKA. “p+” subgroups of KPD have substantial beta cell functional reserve measured >1 month after the index DKA episode, and can discontinue insulin therapy. Either acute beta cell dysfunction leading to DKA is reversible in these patients, or DKA is due to factors other than severe beta cell dysfunction. In a longitudinal study, we measured serum C-peptide, insulin and counter-regulatory hormones in patients with hyperglycemic crises upon admission to the emergency department (ED) to determine beta cell function during the acute DKA episode.

Methods: Among 57 adult patients assessed so far, 32 had DKA (anion gap acidosis with elevated beta-hydroxybutyrate) and 25 had non-ketotic hyperglycemia. Blood was sampled prior to insulin administration in 24 patients (50% with DKA), and <19 h after starting the insulin infusion in 33.

Results: There was no significant difference in C-peptide, glucose, insulin, or cortisol levels in DKA vs. non-ketotic hyperglycemia groups. Mean C-peptide was 1.4 ± 0.5 mg/dl in the DKA group and 2.1 ± 0.4 mg/dl in the non-DKA group (p = 0.29). Among the 24 patients whose blood was sampled prior to administering insulin, there was no group difference in C-peptide levels (2.3 ± 1.2 vs. 2.6 ± 0.7 mg/dl, p = 0.83). C-peptide was >1.5 mg/dl in 22% of the DKA group.

Conclusions: Many adults with KPD have substantial beta cell function at the time of the index DKA episode, a finding that defies the concept that near-complete absence of endogenous insulin secretion is required to develop DKA. Longitudinal follow-up testing will determine whether these patients populate KPD subgroups that are formally defined as "p+"; such an outcome would indicate that their proclivity to develop ketoadiposis may be due to factors other than absence of endogenous insulin, such as defective amino acid metabolism (Patei et al. Diabetes 62:912-922, 2013) or dysregulation of counter-regulatory hormones.

1783-P
Mitochondrial DNA DAMPS Induce Inflammation and Insulin Resistance
LARYSA YUZEFOVYCH, VIKTOR M. FASTUKH, LYUDMILA RACHEK, Mobile, AL
Increasing evidence showed that mitochondrial DNA (mtDNA), as a part of mitochondrial damage-associated molecular patterns (DAMPs), induces an immune response and inflammation in immune, as well as in cells of non-immune origin. As insulin resistance and type 2 diabetes are characterized by a persistent chronic inflammation, the aim if this study was to evaluate if mtDNA DAMPs induce an inflammatory responses in skeletal muscle cells and induce insulin resistance both in vitro and in vivo. In vitro study showed that exogenous mtDNA fragments induced TLR9-mediated NF-κB activation in primary muscle cells. Also, we found that mtDNA DAMPs and palmate increased TLR9 content in muscle cells. Furthermore, mtDNA DAMPs reduced insulin signaling and insulin stimulated glucose uptake in primary muscle cells. Importantly, administration of exogenous mtDNA DAMPs induced inflammatory signaling, hyperglycemia and insulin resistance in vivo, providing a direct causative role for mtDNA DAMPs in the development of insulin resistance. Parallel studies in vivo showed that high fat diet-induced insulin resistant mice (Yuzefovich et al. 2013, PLOS One) have elevated circulating mtDNA DAMPS contents which were associated with increased mtDNA damage in skeletal muscle and liver, increased oxidative stress and content of TLR9 in skeletal muscle. Collectively, this study identifies a novel role for mtDNA as a pro-inflammatory molecule which promotes insulin resistance. Ultimately, this can provide new clinical implications both to design novel therapeutic strategies and cost-effective biomarkers of insulin resistance progression.

Supported By: American Diabetes Association (T13-BS-139-R to L.R.)

1784-P
Modeling the Spectrum of Human Insulin Resistance Using Induced Pluripotent Stem Cells
JASMIN LEBASTCHI, THIAGO M. BATISTA, IVAN CARCAMO-ORIVE, ANNA KROOK, JULEEN R. RIZERATH, JOSH KNOWLES, C. RONALD KAHN, Boston, MA

Induced pluripotent stem cells (iPSCs) represent a unique model to study the genetic components of insulin resistant states in vitro and can be studied in both the undifferentiated and differentiated state. In prior studies we have shown that iPSCs from patients with insulin receptor mutations exhibit altered insulin signaling with reduced insulin-stimulated phosphorylation of IR, IRS, and AKT in IRS-derived myotubes compared to healthy subjects and have reduced insulin stimulation of proliferation and gene expression. We now use iPSCs to characterize the insulin response of type 2 diabetes (T2D) and nondiabetic individuals before and after differentiation to skeletal muscle. The iPSCs from a subgroup of the nondiabetic individuals were further divided into those in the lower and lower quartiles of insulin resistance as

Moderated Poster Discussion

ADA-Supported Research

A474
were indexed on their first claim for any of the basal insulins of interest out any treatment cessation or change to a different basal insulin. Patients formed looking at persistence for T1DM and T2DM patients combined, with insulin detemir (NPH), insulin detemir, and insulin glargine using Canadian private metric. Persistence with antihyperglycemic therapies have been associated baseline to 6 months. However, persistence is another important medication units/mL) delivers the same amount of insulin in one third of the dose. Four identical molecule as insulin glargine (100 unit/mL), insulin glargine (300 unit/mL), insulin glargine (500 unit/mL|lan- tus), 45% insulin detemir 100 IU/|ml (Levemir) and 29% of NPH patients. Conclusion: A retrospective cohort study of real-world claims data demonstrated insulin glargine 300 IU/|ml (Toujeo ™) had the highest persistence among all basal insulins.

1785-P
Dissection of Insulin ‑Dependent Pathways in Skeletal Muscle under Physiological and Diabetic Conditions
THIAGO M. BATISTA, RUBEN GARCIA ‑ MARTIN, WEIKEANG CAI, SUIJIN SUK, HYE LIM NDIH, JASON K. KIM, C. RONALD KAHN, BOSTON, MA, WOCESTER, MA, USA

Insulin signaling regulates growth and metabolism, in part, by regulation of gene expression. To gain more insight into transcriptional pathways activated by physiological levels of insulin in vivo we performed euglycemic insulin clamp in mice at low (4 mU.kg-1.min-1) and high (12 mU.kg-1.min-1) concentrations of insulin and analyzed changes in gene expression in skeletal muscle by RNA ‑sequencing. At 3 h, low insulin regulated 451 genes while high insulin regulated 1771 genes by at least 1.5 ‑fold (FDR<0.25). Interestingly, the most up regulated pathways in muscle were potential targets of estrogen ‑related receptor alpha (Esr1) and were related to TCA cycle and oxidative phosphorylation, while the most suppressed genes were targets of FoxO1 involved in autophagy. Insulin also inhibited the expression of over 40 genes involved in mRNA processing/splicing, mostly within the U2 ribonucleoprotein complex, which regulates the assembly and catalytic activity of the spliceosome. To determine how these insulin ‑dependent pathways might be altered in diabetes, we intersected the clamp gene expression data with gene expression data in streptozotocin (STZ) or high fat diet (HFD) obesity ‑induced diabetes focusing on genes oppositely regulated by insulin and diabetes. This approach revealed 93 insulin ‑regulated genes that were dysregulated in STZ and HFD muscle. Most related to TCA cycle and oxidative phosphorylation, however, changes in mRNAs involved in RNA processing/splicing also overlapped in HFD samples, thus indicating potential insulin ‑resistance ‑specific gene expression signatures. Together these data demonstrate that insulin is a potent regulator of gene expression in vivo altering mRNAs diversity through both changes in expression and dysregulation of the spliceosome, with the latter being most prominent in states of insulin resistance. These differences provide unique targets for therapeutic approaches to type 1 and type 2 diabetes involving muscle. Supported By: National Institutes of Health

1785 ‑P
Persistence with Insulin Glargine 300 IU/ml Compared With Other Basal Insulins—A Canadian Retrospective Cohort Study
KOBINA A. GUANSAH, LUC SIAURIO, ATIF A. KUKASWADIA, SAMANTHA BREMMER, BRADLEY MILLSON, MISSISSAUGA, ON, CANADA; Laval, QC, Canada; Kanata, ON, Canada

Introduction: Insulin glargine (300 units/ml) is a long ‑acting insulin approved in Canada on 28 ‑May ‑2015 for once ‑daily administration in the treatment of T1DM or T2DM requiring basal insulin therapy. Made of the identical molecule as insulin glargine (100 unit/ml), insulin glargine (300 units/ml) delivers the same amount of insulin in one third of the dose. Four pivotal trials compared GLA ‑300 to GLA ‑100 with changes in HbA1c from baseline to 6 months. However, persistence is another important medication metric. Persistence with antihyperglycemic therapies has been associated with positive clinical outcomes and reduced health care costs.

Objective: To assess 12 ‑month persistence on neutral protamine Hagedorn (NPH), insulin detemir, and insulin glargine using Canadian private claims data.

Methods: The study utilized longitudinal private drug plan claims data from IQVIA’s Canadian Private Drug Plan Database. The study was performed looking at persistence for T1DM and T2DM patients combined, without any treatment cessation or change to a different basal insulin. Patients were indexed on their first claim for any of the basal insulins of interest between May 28th 2014 and June 30th 2016, patients’ basal insulin therapy was tracked for 12 months plus a 3 month look ‑forward period. Patients who did not have continuous coverage or with fewer than 3 claims for an insulin were excluded from the analysis. Results: At 12 months using a 80 day grace period, 63% of insulin glargine 300 IU/ml (Toujeo ™) patients persisted with therapy compared to 54% of insulin glargine 100 IU/ml(Basaglar), 50% for insulin glargine 100 IU/ml (Lan­ tus), 45% insulin detemir 100 IU/ml (Levemir) and 29% of NPH patients. Conclusion: A retrospective cohort study of real ‑world claims data demonstrated insulin glargine 300 IU/ml (Toujeo ™) had the highest persistence among all basal insulins.

1786 ‑P
Adipocyte Overexpression of p55x Subunit of PI3K Improves Systemic Glucose Metabolism in Lean Mice
ZACHARY S. CLAYTON, CARRIE MCCURDY, Eugene, OR

Phosphatidylinositol 3 ‑kinase (PI3K), a heterodimeric enzyme composed of a regulatory subunit p85α/γ, p55x/γ, p50α and a catalytic subunit p110α/β, is an essential component of the canonical insulin signaling cascade in adipose tissue. Insulin ‑stimulated PI3K activity is decreased in obese adipose tissue in parallel with a 4 ‑fold increase in p55x abundance, heterogeneous deletion of P43r1 limits regulatory subunit expression and enhances adipocyte insulin signaling and decrease systemic glucose tolerance. To test this hypothesis, we generated mice with p55x knock ‑in at the endogenous ROSA26 locus. The recombinant cassette was made by flanking the p55x cDNA and a floxed 4x SV40 poyA STOP signal with FRT and F3. The insertion of P43r1 at the ROSA26 locus mediated by Flit recombinase in ES cells targeted with FRT ‑PI3K ‑neo ‑F3 at the ROSA26 locus. The polyA STOP signal was removed by crossing the p55x flox (Fl/F) mice with carrying Adipo ‑cre recombinase (DOX). At 12 weeks of age, the metabolic phenotype, glucose tolerance and adipocyte insulin signaling were measured in F/L and OX mice. In adipose tissue, p55x abundance was 7 ‑fold higher in OX compared to F/L controls with no difference detected in p85x abundance. Body weight and adiposity was not different between F/L and OX mice. Food intake, energy expenditure and the respiratory quotient were not different in OX vs. F/L, despite a decrease in total activity in OX mice. Contrary to our hypothesis, glucose AUC calculated from oral glucose tolerance tests was 40% lower (P<0.005) in OX vs. F/L. Overall these data suggest that increased expression of the p55x regulatory subunit, in contrast to p85x, enhances PI3K activity and insulin signaling in adipocytes.

Supported By: Eugene and Olivia Evonuk Memorial Graduate Fellowship; University of Oregon (to Z.S.C.) National Institute of Diabetes and Kidney Diseases (R01DK095526 to C.M.)

1788 ‑P
MEDI0382, a GLP ‑1/Glucagon Receptor Dual Agonist, Enhances Leptin ‑Mediated pSTAT3 Induction in Key Neuronal Regions That Regulate Metabolism
HANNES JOHANN, PERNILLE BARKHOLT, RIKKE GRÜNLUND, JAMES TREVASKIS, Gaithersburg, MD, Hørsholm, Denmark

MEDI0382 is a potent GLP ‑1 and glucagon receptor dual agonist peptide that decreases body weight of obese mice by reducing food intake and enhancing energy expenditure. Here we explored whether MEDI0382 may, that decreases body weight of obese mice by reducing food intake and enhancing energy expenditure. Here we explored whether MEDI0382 may, in part, mediate its effects on metabolism by enhancing leptin action. Diet ‑induced obese mice were administered vehicle, MEDI0382 (10 nmol/kg; s.c., q.d.) or vehicle and pair ‑fed to MEDI0382 ‑treated mice for 10 days (n=15/16 group). During this period MEDI0382 induced 11% body weight loss (p<0.01 vs. vehicle), whereas pair ‑fed mice lost a similar amount of body weight as MEDI0382 group for first 5 days, but rebounded such that final weight loss was 3% from baseline (p<0.05 vs. vehicle and MEDI0382). On day 10, half of each group was administered vehicle (PBS) or murine leptin (10 mg/kg) and the mice sacrificed 45 min later. Leptin administration increased circulating leptin levels 20 ‑25 ‑fold above endogenous levels. Levels of phosphorylated STAT3 (pSTAT3), a key marker of leptin signaling, were determined in discrete nuclei of the hypothalamus known to regulate energy homeostasis. Within the arcuate nucleus of the hypothalamus pSTAT3 levels were not sig-
were indexed on their first claim for any of the basal insulins of interest out any treatment cessation or change to a different basal insulin. Patients formed looking at persistence for T1DM and T2DM patients combined, with baseline to 6 months. However, persistence is another important medication pivotal trials compared GLA-300 to GLA-100 with changes in HbA1C from units/mL) delivers the same amount of insulin in one third of the dose. Four treatment of T1DM or T2DM requiring basal insulin therapy. Made of the approved in Canada on 28-May-2015 for once-daily administration in the ...

**1786-P**

**Dissection of Insulin-Dependent Pathways in Skeletal Muscle under Physiological and Diabetic Conditions**

THAILOI M. SATIYAG, RUBIN KADIMO, MARVIN WANG, CAI SHIUN, SUI YIE LIN NGH, JASON K. KIM, C. ROLAND KAHN, BOSTON, MA, WYOMING, WY, M4

Insulin signaling regulates growth and metabolism, in part, by regulation of gene expression. To gain more insight into transcriptional pathways activated by physiological levels of insulin in vivo we performed euglycemic insulin clamp in mice at low (4 mU.kg⁻¹.min⁻¹) and high (12 mU.kg⁻¹.min⁻¹) concentrations of insulin and analyzed changes in gene expression in skeletal muscle by RNA-sequencing. At 3 h, low insulin regulated 451 genes while high insulin regulated 1771 genes by at least 1.5fold (FDR<0.25). Interestingly, the most up regulated pathways in muscle were potential targets of estrogen-related receptor alpha (Esr1) and were related to TCA cycle and oxidative phosphorylation, while the most suppressed genes were targets of FoxO1 involved in autophagy. Insulin also inhibited the expression of over 40 genes involved in mRNA processing/splicing, mostly within the U2 ribonucleoprotein complex, which regulates the assembly and catalytic activity of the spliceosome. To determine how these insulin-dependent pathways might be altered in diabetes, we intersected the clamp gene expression data with gene expression data in streptozotocin (STZ) or high fat diet (HFD) obesity-induced diabetes focusing on genes oppositely regulated by insulin and diabetes. This approach revealed 93 insulin-regulated genes that were dysregulated in STZ and HFD muscle. Most related to TCA cycle and oxidative phosphorylation, however, changes in mRNAs involved in RNA processing/splicing also overlapped in HFD samples, thus indicating potential insulin-resistance-specific gene expression signatures. Together these data demonstrate that insulin is a potent regulator of gene expression in vivo altering mRNA diversity through both changes in expression and dysregulation of the spliceosome, with the latter being most prominent in states of insulin resistance. These differences provide unique targets for therapeutic approaches to type 1 and type 2 diabetes involving muscle.

**Supported By: National Institutes of Health**

**1787-P**

**Adipocyte Overexpression of p55cx Subunit of PI3K Improves Systemic Glucose Metabolism in Lean Mice**

ZACHARY S. CLAYTON, CARRIE MCCURDY, Eugene, OR

Phosphatidylinositol 3-kinase (PI3K), a heterodimeric enzyme composed of a regulatory subunit (p85α/p55cx/p50α) and a catalytic subunit (p110α/p110β), is an essential component of the canonical insulin signaling cascade in adipose tissue. Insulin-stimulated PI3K activity is decreased in obese adipose tissue in parallel with a 4-fold increase in p55cx abundance, heterozygous deletion of PI3r1 limits regulatory subunit expression and enhances adipocyte insulin signaling. Additionally, genetic deletion of p55cx/p50α in mice has been shown to increase adipocyte glucose uptake and systemic insulin sensitivity. Therefore, we hypothesized that adipocyte-specific p55cx overexpression (OX) would rescue adipocyte insulin signaling and decrease systemic glucose tolerance. To test this hypothesis, we generated mice with p55cx knock-in at the endogenous ROSA26 locus. The recombination cassette was made by flanking the p55cx CDA and a floxed 4x SV40 polyA STOP signal with FRT and F3. The insertion of F3r1 at the ROSA26 locus mediated by Fis-recombinease in ES cells targeted with FRT-PIK-neo-F3 at the ROSA26 locus. The polyA STOP signal was removed by crossing the p55cx flox (F/F) mice with carrying Adipoq-cre recombinase (OX). At 12 weeks of age, the metabolic phenotype, glucose tolerance and adipocyte insulin signaling were measured in F/F and OX mice. In adipose tissue, p55cx abundance was 7-fold higher in OX compared to F/F controls with no difference detected in p58α abundance. Body weight and adiposity was not different between F/F and OX mice. Food intake, energy expenditure and the respiratory quotient were not different in OX vs. F/F, despite a decrease in total activity in OX mice. Contrary to our hypothesis, glucose AUC calculated from oral glucose tolerance tests was 40% lower (P=0.005) in OX vs. F/F. Overall these data suggest that increased expression of the p55cx regulatory subunit, in contrast to p55α, enhances PI3K activity and insulin signaling in adipocytes.

**Supported By: Eugene and Da Evansk Memorial Graduate Fellowship; University of Oregon (to Z.S.C.); National Institute of Diabetes and Kidney Diseases(R01DK095926 to C.M.)**

---

**INTEGRATED PHYSIOLOGY—CENTRAL NERVOUS SYSTEM REGULATION OF METABOLISM**

---

**1876-P**

**Persistence with Insulin Glargine 300 IU/ml Compared With Other Basal Insulins—A Canadian Retrospective Cohort Study**

KOBINA A. GUANSAH, LUC SCAURIOL, ATIF A. KUKUSWAIAH, SAMANTHA BRENNER, BRADLEY MILLSON, MISSISSAUGA, ON; Canada, Laval, QC; Canada, Kanata, ON, Canada

Introduction: Insulin glargine (300 units/ml) is a long-acting insulin approved in Canada on 28-May-2015 for once-daily administration in the treatment of T1DM or T2DM requiring basal insulin therapy. Made of the identical molecule as insulin glargine (100 units/ml), insulin glargine (300 units/ml) delivers the same amount of insulin in one third of the dose. Four pivotal trials compared GLA-300 to GLA-100 with changes in HbA₁c from baseline to 6 months. However, persistence is another important medication metric. Persistence with antihyperglycemic therapies has been associated with positive clinical outcomes and reduced health care costs.

Objective: To assess 12-month persistence on neutral protamine Hagedorn (NPH), insulin detemir, and insulin glargine using Canadian private claims data.

Methods: The study utilized longitudinal private drug plan claims data from IQVIA’s Canadian Private Drug Plan Database. The study was performed looking at persistence for T1DM and T2DM patients combined, without any treatment cessation or change to a different basal insulin. Patients were indexed on their first claim for any of the basal insulins of interest between May 28th 2014 and June 30th 2016, patients’ basal insulin therapy was tracked for 12 months plus a 3 month look-forward period. Patients who did not have continuous coverage or with fewer than 3 claims for an insulin were excluded from the analysis.

Results: At 12 months using a 90 day grace period, 63% of insulin glargine 300 IU/ml (Toujeo®) patients persisted with therapy compared to 54% of insulin glargine 100 IU/ml (Basaglar), 50% for insulin glargine 100 IU/ml (Lantus), 45% insulin detemir 100 IU/ml (Levemir) and 29% of NPH patients.

Conclusion: A retrospective cohort study of real-world claims data demonstrated insulin glargine 300 IU/ml (Toujeo®) had the highest persistence among all basal insulins.

---

**1878-P**

**MEDI0382, a GLP-1/Glucagon Receptor Dual Agonist, Enhances Leptin-Mediated pSTAT3 Induction in Key Neuronal Regions That Regulate Metabolism**

HANNI JOURHAN, FERNILLE BARKHOLT, RIKKE GRÖNLUND, JAMES TREVASKIS, Gaithersburg, MD, Harholm, Denmark

MEDI0382 is a potent GLP-1 and glucagon receptor dual agonist peptide that decreases body weight of obese mice by reducing food intake and enhancing energy expenditure. Here we explored whether MEDI0382 may, in part, mediate its effects on metabolism by enhancing leptin action. Diet-induced obese mice were administered vehicle, MEDI0382 (10 nmol/kg; s.c., q.d.) or vehicle and pair-fed to MEDI0382-treated mice for 10 days (n=15/16/group). During this period MEDI0382 induced 11% body weight loss (p<0.01 vs. vehicle), whereas pair-fed mice lost a similar amount of body weight as MEDI0382 group for first 5 days, but rebounded such that final weight loss was 3% from baseline (p=0.05 vs. vehicle and MEDI0382). On day 10, half of each group was administered vehicle (PBS) or murine leptin (10 mg/kg) and the mice sacrificed 45 min later. Leptin administration increased circulating leptin levels 20-25-fold above endogenous levels. Levels of phosphorylated STAT3 (pSTAT3), a key marker of leptin signaling, were determined in discrete nuclei of the hypothalamus known to regulate energy homeostasis. Within the arcuate nucleus of the hypothalamus pSTAT3 levels were not sig-

---

**INTEGRATED PHYSIOLOGY—CENTRAL NERVOUS SYSTEM REGULATION OF METABOLISM**

---

**POSTERS**

---

**ADA-Supported Research**

**Moderated Poster Discussion**

---

**A475**
Effect of Bariatric Surgery on Neuroplasticity in Humans

GIUSEPPE DANIELE, ANGELA DARDANO, CLAUDIA LUNghi, PAOLA BINDA, ANNAMARIA CICCARENA, FERRUCCIO SANTINI, GIOVANNI CECCHARINi, LAURA GIUSTI, ROSARIO BELUNi, MARIA SEGHERI, OLIVIA DEL GUERRA, CARLO MORETTO, MARIA CONCETTA MORRONE, STEFANO DEL PRATO, GIUSEPPE SULIKOWSKI, ARTHUR R. LEWIS, JAMES TREVASKIS, DAVID BAKER, BRIAN MAHoney, JOE YOUNG, KIM, C. RONALD KAHN, MARK BARTLETT, ANGELO LA FRETA, VIRGINIA DELGADO, EMIL JONSSON, CARLO GIUSTI, ROSARIO BELLINI, MARTA SEGHIERI, SILVIA DEL GUERRA, CARLO MORETTO, MARIA CONCETTA MORRONE, STEFANO DEL PRATO, Pisa, Italy

Background and Aim: Obesity and diabetes are associated to increased risk of cognitive impairment, neurodegenerative disorders, neuroinflammation and synaptic plasticity abnormalities. The aim of the study was to evaluate the effect of obesity and bariatric surgery on neural plasticity (NP).

Methods: We recruited 20 normal weight subjects (NS; age 26±10 years, BMI 21.7±2.6 kg/m²) and 31 obese subjects (OB; 40±11 years; BMI: 41±6.7 kg/m²) in whom the neural plasticity was measured as change in ocular dominance after 120 min of monocular deprivation obtained by ocular patch. To explore the effect of body weight reduction on NP, 14 OB (BMI=45±1.8 kg/m²) underwent metabolic surgery (RYGB) and NP was measured 6 months after surgery. Hormonal and metabolic parameters were obtained before and after administration of 75g glucose (OGTT).

Results: At baseline NP was lower in OB than in NS (0.04±0.08 vs. 0.12±0.05, p=0.003). NP was inversely correlated with body weight (r= -0.33, p<0.001). Six months after RYGB, BMI was markedly reduced (34.3±1.6 kg/m²); p=0.001 vs. baseline) and glucose metabolism improved (HOMA-IR from 4.7±0.9 to 1.6±0.4; P=0.006 and Disposition Index from 0.07±0.02 to 0.81±0.30 mU·min/kg·m²). NP was correlated with body weight (r= -0.55; p<0.001) and brain plasticity (r=0.86; p<0.007) and BMI reduction (r=0.10; p=0.07).

Conclusion: NP is markedly altered in OB, and it is restored to normal after RYGB. The relationship between NP increase and circulating glucose levels may suggest a potential role of this hormone in the NP restoration in humans.

Integrated Physiology/CENTRAL NERVOUS SYSTEM REGULATION OF METABOLISM

1792-P

Insulin Acutely Regulates Gene Expression in Brain—A New Potential Major Level of Control of Metabolism and Neurotransmission

WEIKANG CAI, ALFREDO RAMIREZ, JONATHAN DREYFUSS, THAIGO M. BATISTA, RUBEN GARCIA MARTIN, HUI PAN, MENGYAO E. LI, BRIAN D. O’NEILL, JASON K. KIM, C. RONALD KAHN, BOSTON, MA, Iowa City, IA, Worcester, MA

While the brain is now recognized as an insulin sensitive tissue, and impaired insulin signaling in brain can lead to many metabolic and behavioral abnormalities, effects of insulin on gene expression in the brain remain largely unknown. To understand now this aspect of insulin action may impact physiology in vivo, we performed hyperinsulinemic-euglycemic clamps at low (4 µU/kg/min) and high (12 µU/kg/min) physiological doses of insulin in C57Bl/6J mice, and after 3 hours collected different brain regions and analyzed their transcriptomes using RNA Seq. In response to low dose insulin infusion, 1851 genes were up- or down-regulated in the hypothalamus by at least 50% (all P < 0.01). This was more than 4-fold as the number of genes regulated in liver or muscle under the same conditions. Other regions showed different responses with 205 significantly regulated by at least 50% in hippocampus and 131 regulated in normal accumbens. The most upregulated pathway in all three regions was that for very long chain fatty acyl-CoA synthesis, indicating an important role of insulin action on brain fatty acid metabolism. Most other insulin responsive

1790-P

Glucose Uptake in Muscle, Visceral Adipose Tissue, and Brain Strongly Predict Whole-Body Insulin Resistance in the Development of Type 2 Diabetes

GRETHA J. BOERSMA, KERSTIN HEURLING, MARIA J. PEREIRA, EMIL JOHANSSON, MARK BARTLETT, ANGELO LA FRETA, VIRGINIA DELGADO, EMIL JONSSON, CARLO GIUSTI, ROSARIO BELLINI, MARTA SEGHIERI, SILVIA DEL GUERRA, CARLO MORETTO, MARIA CONCETTA MORRONE, STEFANO DEL PRATO, Pisa, Italy

Background and Aim: Obesity and metabolic syndrome in humans is strongly associated with insulin resistance. Insulin resistance is known to be regulated by both peripheral and central mechanisms. Whole-body insulin resistance is associated with insulin signaling abnormalities in brain. The aim of the study was to elucidate tissue-specific glucose uptake in the development of type 2 diabetes.

Methods: We aimed to elucidate tissue-specific glucose uptake in the development of type 2 diabetes. MEDI0382, a GLP-1/glucagon receptor dual agonist, shows different patterns of activation vs. liraglutide and G1432. MEDI0382 reduces food intake and body weight in obese mice and primates. In rodents, the weight-reducing effects of MEDI0382 are superior to those of the GLP-1 analogue, liraglutide. The current study characterised the activation of distinct neuroanatomical areas following peripheral administration of MEDI0382, relative to liraglutide and the glucagon receptor agonist, G1432.

Results: While the brain is now recognized as an insulin sensitive tissue, and impaired insulin signaling in brain can lead to many metabolic and behavioral abnormalities, effects of insulin on gene expression in the brain remain largely unknown. To understand now this aspect of insulin action may impact physiology in vivo, we performed hyperinsulinemic-euglycemic clamps at low (4 µU/kg/min) and high (12 µU/kg/min) physiological doses of insulin in C57Bl/6J mice, and after 3 hours collected different brain regions and analyzed their transcriptomes using RNA Seq. In response to low dose insulin infusion, 1851 genes were up- or down-regulated in the hypothalamus by at least 50% (all P < 0.01). This was more than 4-fold as the number of genes regulated in liver or muscle under the same conditions. Other regions showed different responses with 205 significantly regulated by at least 50% in hippocampus and 131 regulated in normal accumbens. The most upregulated pathway in all three regions was that for very long chain fatty acyl-CoA synthesis, indicating an important role of insulin action on brain fatty acid metabolism.
genes in these three brain regions were distinct. In the hypothalamus, insulin played a key role in modulating genes involved in neurotransmission in the hypothalamus, including enhancing the GABA A receptor signaling pathway and suppressing neuropeptide signaling pathways. Insulin also modulated metabolism in the hypothalamus by suppressing the glycolysis and pentose phosphate pathways, while increasing the pyruvate dehydrogenase complex and cholesterol biosynthesis. Thus, insulin action in the brain acutely and potently regulates expression of genes involved in brain metabolism, neurotransmission and neuromodulation. In this way, insulin re-routes the carbon source to the biogenesis of plasma membrane for neuronal and glial function and synaptic remodeling.

Improving Sleep by Trazodone Improves Glucose Control

SAAID SAKKAL, Milton, FL

Background: 77% of people with diabetes have some form of insomnia. Sleep disturbance results in impaired glucose control in healthy individuals or worsens glucose control in people with diabetes. Short-term sleep studies (1-6 weeks) improved glucose control and insulin resistance in obese “healthy” individuals. We have shown before the superior benefit Trazodone has in treating neuropathy over gabapentin. We show, in this abstract, the impact of improving sleep may have on glucose control.

Methods: We treated 200 type 2 patients with diabetic neuropathy with either trazodone (100), or Gabapentin (100), compared the change in neuropathy, sleep and glucose control. We quantified their neuropathy with our previously published neuropathy grading system (Sakkal’s Scale: level of vibration sensory loss by the 128 tuning fork) we quantified their sleep with shortening latency of sleep onset, and sleep duration extension. We measured their glucose control with AM insulin-to-glucose ratio, HgA1c, and in-target glucose when CGMS (20 patients). We excluded patients with OSA. All patients followed our standard diabetes treatment protocol for type 2.

Results: At 12 months, Trazodone improved the scale of diabetic neuropathy in 80% of patients, sleep hygiene in 70%, Sleep improved by 40 minutes, and sleep onset latency decreased by 10 minutes. Insulin/glucose ratio was 0.71±0.147, HgA1c 7.2%, in-target glucose in 72% on CGMS (12 patients). Gabapentin improved the scale of diabetic neuropathy in 66%, sleep hygiene in 44%; with sleep increasing by 14 minutes, and sleep onset latency decreased by 4 minutes. Insulin-to-Glucose ratio was 33.56±0.19, HgA1c 7.8%, HgA1c 7 in 56%, and in-target-glucose in 58% on CGMS (8 patients.) analysis. A maximum number of diabetes medications used were 3 in both groups. Percentage needing basal insulin at the end was 12% in the Trazodone group, 21% in the Gabapentin group.

Conclusion: Improved sleep and neuropathy with Trazodone improved glucose control.

DJB Surgery Improved the T2DM Rats Glucose Homeostasis, Elevated the Glucose Utilization, and the GLUT3 Expression in Brain

RUYIAN PAN, NA LI, TINGXUN ZHAO, HUAJIE WANG, BIN JIANG, HUAIJIE WANG, NA LI, TINGKUN ZHAO, CHUNMEI WANG, YANLIN HE, PINGWEN XU, YONGJIE YANG, YONG XU, HONG YAN, ZHIQIN GAO, MEI-HUA QU, Weifang, China

Duodenal-jejunal bypass surgery (DJB) is an experimental surgical procedure to study the mechanism of gastric surgery in T2DM treatment.

Methods: T2DM rats induced by high glucose high fat food and low dose streptozotocin (STZ) injection were randomly divided into 2 groups: T2DM-DJB. Wistar rats were used as normal control. The fasting blood glucose and HbA1C were measured. Glucose utilization, and the GLUT3 expression in the brain were measured by Q-RT-PCR.

1.55±0.31, P<0.001). Q-RT-PCR showed that GLUT3 expression in the brain significantly increased 4 weeks after DJB while T2DM rats decreased. This study indicates that the improvement of glucose utilization in the brain plays a pivotal role in DJB treatment of T2DM.

Conclusion: DJB surgery improved T2DM rats glucose homeostasis, elevated the glucose utilization, and the GLUT3 expression in brain was elevated significantly 4 weeks after DJB. DJB surgery improved the glucose utilization in the brain was significantly elevated significantly 4 weeks after DJB while T2DM rats decreased. This study indicates that the improvement of glucose utilization in the brain plays a pivotal role in DJB treatment of T2DM.
also decreased in mice lacking Tap63 in POMC neurons. Collectively, Tap63 in mature POMC neurons regulates glucose homeostasis and Tap63 is one key molecular driver for the sexual dimorphism in energy homeostasis.

**1797-P**

**Hierarchical Brain and Physiological Responses to Hypoglycemia and HAIF**

**JOHN J. LEE, AARON TANENBAUM, ANA MARIA ARBELAEZ, HIERARCHICAL BRAIN AND PHYSIOLOGICAL RESPONSES TO HYPOGLYCEMIA AND HAIF IN T1DM STUDY GROUP, St. Louis, MO**

Glycemic control is essential for the management of diabetes. However, intensive glycemic control brings increased morbidity and mortality associated with hypoglycemia. This work tested the hypothesis that human brain networks have functional patterns of hierarchical recruitment in physiological responses to induced hypoglycemia.

Methods: Sixty-nine age and gender matched subjects (28, T2DM, 17, T2DM+MCI (T2DM/MCI) and 29, healthy volunteers (HV)) were randomized to receive saline or regional CBF changes in subjects with T2DM and MCI. Results: The thalamus, medial prefrontal (MPFC) and orbital prefrontal cortices (OPFC), and striatum have differential changes in CBF with progressive hypoglycemia. Significance was verified using threshold-free cluster enhancement methods.

Discussion: With progressively induced hypoglycemia, specific cortical and subcortical regions demonstrate characteristic alterations of CBF. These changes confirm existing data regarding the roles of the thalamus, MPFC, OPFC and striatum in responses to hypoglycemia. Furthermore, regional CBF reactivity to progressive, induced hypoglycemia has distinctive features for acute/recurrent hypoglycemia and hypoglycemia in T1DM: These characteristic features suggest mechanistic roles for human brain networks in physiological responses to severe hypoglycemia and hypoglycemia-associated autonomic failure (HAIF). **Figure.**

**1798-P**

**Cerebral Blood Flow Abnormalities in Brain Regions Responsible for Cognitive Function in Type 2 Diabetes**

**LEANNE HUNT, DINESH SELVARAJAH, SOLOMON TESFAYE, IAIN D. WILKINSON, Sheffield, United Kingdom**

**Aim:** The risk of developing mild cognitive impairment (MCI) increases with type 2 diabetes (T2DM). Brain morphometric changes associated with MCI have been described. However, Cerebral Blood Flow (CBF) changes in relation to MCI has not been fully investigated. This study aims to investigate regional CBF changes in subjects with T2DM and MCI.

Method: Seventy-four age and gender matched subjects (28, T2DM (T2DM); 17, T2DM+MCI (T2DM/MCI) and 29, healthy volunteers (HV)) were recruited. All subjects underwent clinical and questionnaire (Addenbrooke’s Cognitive Assessment [ACE-R]) assessment along with Arterial Spin Labeling (ASL) perfusion Magnetic Resonance Imaging (MRI) of the brain. The ASL data was modelled to yield quantitative arterial CBF maps in neuroanatomical regions involved with cognitive function. Results: Demographic data revealed aged-matched participants between all three groups (mean age 65.4 ± 15.5 years, ANOVA, p = 0.16). Mean age of last education was significantly lower in the T2DM/MCI group (mean ± SD; 15.1 ± 0.9 when compared to the other groups (HV 19.3 ± 5.6, T2DM 17.1 ± 2.9) Kruskal-Wallis, p = 0.003. T2DM/MCI ACE-R score (mean ± SD; 83 ± 4) was significantly lower compared to other groups (HV = 96 ± 2, T2DM = 94 ± 3, ANOVA p<0.001). There was significantly lower CBF in T2DM/MCI compared to T2DM and HV in the medial temporal lobes (CBF 76.8 ± 100/ min, ANOVA p<0.05),insula (CBF 67.5 ml/100g/min ANOVA p<0.05), and frontal lobes (CBF 71.8 ml/100g/min, ANOVA p<0.05). Pearson’s correlation revealed significant correlations between ACE-R score and regional CBF measurements in the medial temporal lobes, (p<0.05, r=−0.25) thalamus (p<0.05, r=−0.23) and insula (p<0.05, r=−0.29).

Conclusion: This study demonstrates significantly lower CBF in T2DM/MCI subjects in neuroanatomical regions responsible for cognitive function. This may be essential to help understand the pathological mechanisms that occurs behind the increased risk of developing cognitive impairment in T2DM.

**Discussion.**

**1800-P**

**Hypothalamic Sphinex and Galanin Receptor 2 Are Novel Regulators of Energy Balance in Mice**

**NA-HEE HA, NAM HOON KIM, CHANG-HOON KIM, MUN-GYU SONG, HYE-JIN LEE, BO-YEONG JIN, MI-RAE PARK, JAE YOUNG SEONG, SIN GON KIM, DONG-MOON KIM, Seoul Republic of Korea**

Sphinex is a novel neuropptide discovered by bioinformatic and has been proposed as a regulator of energy balance. However, its precise role and underlying mechanisms remain unclear. In this study, we investigated the role of sphinex and its receptor, galanin receptor 2 (GALR2), in regulation of energy balance in the mediodorsal hypothalamus of mice. Administration of sphinex into the third ventricle near the hypothalamus (iV) significantly decreased food intake and body weight with no change in energy expenditure in mice. The central sphinex-induced anorexia and weight loss were reinstated by pre-i3V administration of GALR2 antagonist, M871, indicating hypothalamic GALR2-mediated action of sphinex in the regulation of energy balance.
balance. In addition, we showed that 12V administration of spexin-based selective GALR2 agonist significantly reduced food intake and body weight in a dose-dependent manner with no signs of illness assessed by a conditioned taste aversion test, suggesting a novel role of hypothalamic GALR2 in the regulation of energy balance. Furthermore, we found that activation of GALR2 induced by spexin increased phosphorylation of CREB in the mediodi- basal hypothalamus of mice and cells overexpressing GALR2 different from galanin, suggesting a ligand-dependent switch of G protein coupled with GALR2. Taken together, these results suggested a critical role of hypothalamic spexin and GALR2 in the regulation of energy balance in mice.

1802-P
Short-Term Weight Loss Undermines Brain Regulation of Food Consumption
WAI LAM, DONGJU SEO, CHERYL LACADIE, CHRISTIAN P. SCHMIDT, SAMUEL ROSENBERG, HAI HOANG, JANICE HWANG, TODD CONSTABLE, MARY SAVOYE, RAJITA SINHA, ROBERT SHERWIN, RENATA BELFORT-DEAGUIAR, ANDREAS L. BIRKENFELD, DIETMAR SCHMIDT
The mitochondrial chaperones heat shock protein 10 (HSP10) and 60 enable proper protein folding and thereby facilitate mitochondrial function. Previously, we demonstrated a reduction of hypothalamic Hsp60 gene expression in type 2 diabetic mice and patients which caused mitochondrial dysfunction and central insulin resistance. Mitochondrial HSP10 is also reduced in brains of db/db mice. However, the effects of reduced HSP10 expression in brain on metabolism and insulin sensitivity are unknown. Thus, we generated a shRNA-mediated knockdown (KD) of Hsp10 in the hypothalamic murine cell line Clu1B3 and investigated cellular stress responses, mitochondrial function and insulin signaling. 50% KD of HSP10 in vitro causes impaired mitochondrial dynamics and reduced mitochondrial count, but increases mitochondria-endoplasmatic reticulum (ER) contact sites. These cells exhibit reduced mitochondrial respiration and mild oxidative stress represented by a 35% decrease of protein amount of SOD2 along with about 20% decreased protein amounts of subunits of the electron transport chain complexes IV and V. Notably, HSP10 KD induces ER stress shown by the increased gene expression of Chop and increased phosphorylation of IRE1(S724). Most importantly, KD of HSP10 induces acute insulin resistance shown by reduced phosphorylation of IRS-1(Y612) and Akt1/2(PKBoS473) after 5 min of 10 nM insulin stimulation. Preliminary data of a lentiviral-mediated KD approach of Hsp10 in the mediodi-basal hypothalamus in C57BL/6N mice revealed an unexpected 11% reduction in liver weight partly due to reduced hepatic glycogen content compared to control mice. Consistently, hepatic expression of Pepck, which is suppressed by insulin, was increased in Hsp10 KD mice by 60%.

In conclusion, we identified an unexpected role of Hsp10 in regulating hypothalamic mitochondrial function, insulin sensitivity and liver function. Thus, hypothalamic Hsp10 may present a novel regulator of the brain-liver crosstalk.

Supported By: Deutsche Forschung Gemeinschaft; Deutsches Zentrum fuer Diabetes Forschung

1803-P
Central K ATP Channels Modulate Glucose Effectiveness
WILLIAM G. MITCHELL, ERIC LONTCHI-YIMAGOU, SARAH A. REDA, MICHÈLE CAREY, KEHAI ZHANG, SANDRA ALEKSIC, DEREK HUFFMAN, MEREDITH WILLIAM G. MITCHELL, ERIC LONTCHI-YIMAGOU, SARAH A. REDA, MICHELLE CAREY, KEHAI ZHANG, SANDRA ALEKSIC, DEREK HUFFMAN, MEREDITH HAWKINS, BARDEN HAWKINS, BARDEN HAWKINS, BARDEN HAWKINS, BARDEN HAWKINS, BARDEN
Glucose effectiveness describes the restraining effect of hyperglycemia on endogenous glucose production (EGP), which is lost in type 2 diabetes (T2D). Since central nervous system KATP channels likely regulate EGP in humans and rats, we examined whether these channels contribute to glucose effectiveness. Paired 4-hour hyperglycemic ‘pancreatic clamp’ studies were performed in 9 healthy humans (age 37 ± 15 years; BMI 26.4 ± 4.7 kg/m2) 3 hours following glyburide 10 mg (GLB) or placebo (PLC). With PLC, hyperglycemia suppressed EGP by 59% (egulogenic: 2.38 ± 0.29 vs. hyperglycemia: 0.98 ± 0.17, p < 0.001). GLB resulted in 46% less suppression of EGP by hyperglycemia from baseline egulogenic compared to PLC (GLB: 1.56 ± 0.29 mg/kg/min vs. PLC: 0.98 ± 0.17 mg/kg/min, p = 0.047). To confirm that GLB’s effects were centrally mediated, parallel hyperglycemic studies were conducted in normal rats after oral gavage of normal saline (NS) (n=8), GLB (n=14), and oral GLB with intracerebroventricular (ICV) infusion of KATP channel agonist diazoxide (DZX) (n=8). GLB attenuated hyperglycemia’s suppressive effect on EGP (GLB: 8.4 ± 0.3 mg/kg/min vs. NS: 6.9 ± 0.3 mg/kg/min; p = 0.047), while ICV DZX abolished the effects of GLB (DZX + GLB: 5.5 ± 0.5 mg/kg/min vs. GLB, p = 0.003) (Figure 1). This suggests that ~50% of the suppression of EGP by hyperglycemia is mediated by central KATP channels. Targeting these channels may offer a new therapeutic approach to improve glycemic control in T2D.

Supported By: National Institutes of Health

1804-P
Neuronal Deletion of the Mammalian Indy Homolog (Slc13a5) Increases Energy Expenditure in Mice
ANICA KURZBACH, DIANA M. WILLMES, TINA SCHUMANN, CHRISTINE HENKE, NERMEEN EL-AGROUDY, ANDRE KLEINRIDDERS, ANDREAS L. BIRKENFELD, DIETMAR SCHMIDT
INDY (I’m Not Dead Yet) is a transporter of TCA cycle intermediates, mediating cellular citrate uptake and is highly expressed in liver and brain.
Reduced expression of Indy in lower organisms extended lifespan, reduced whole body fat content and increased mitochondrial biogenesis. In mammals, whole body deletion of the mammalian Indy homolog (mIndy, Slc13a5) is less susceptible to diet-induced obesity and insulin resistance. Here, we address the role of neuronal mIndy in energy homeostasis. We generated a neuronal mIndy knockout (NINKO) mouse model by crossing mIndy-foxed to NestinCre mice. Deletion of mIndy in neurons led to an increase in energy expenditure compared to NestinCre mice after 8 weeks of high fat diet (HFD) feeding (average 24 h EE: NestinCre: 11.5±0.5 kcal/kg lean mass (im); NINKO: 13.6±0.6 kcal/kg im; p<0.01). The respiratory exchange ratio decreased from 0.79±0.01 in NestinCre mice to 0.77±0.01 in NINKO mice during the light phase (p<0.001), indicating augmented lipid oxidation in NINKO mice. Body temperature increased in NINKO compared to NestinCre mice (NestinCre: 37.0±0.1°C; NINKO: 37.3±0.1°C at 6pm; p<0.05). Fat mass was reduced and lean mass increased significantly in NINKO mice (NestinCre: 60±1% im, 31±1% fat mass; NINKO: 68±1% im, 27±1% fat mass after 8 weeks of HFD feeding; p<0.05). Hyperinsulinemic-euglycemic clamp studies showed improved insulin sensitivity in NINKO mice (steady state GINF NestinCre: 26±2 mg/kg/min; NINKO: 36±2 mg/kg/min; p<0.05). Together, these data suggest that neuronal mIndy is a critical regulator of energy and glucose homeostasis in mammals. Further studies will address the mechanisms involved in the effect.

1805-P Novel Function of Increased Ventromedial Hypothalamus (VMH) Norepinephrine (NE) to Block Local VMH Hyperglycemia Sensing Coupled to Increased Insulin Action CARL STOELZEL, ANTHONY CICOTTO, Tewton, RI

It is well established that local glucoprivation at the VMH stimulates glucoregulatory neurons and acute neuregulatory activity (NA) therein necessary for the sympathoadrenal counter regulatory response to such glucoprivation. However, paradoxically a wide variety of insulin resistant, glucocorticoid, hyperglycemic animal models exhibit chronic elevation of NA at the VMH. Further, chronic VMH infusion of NE to normal animals leads to insulin resistance and glucoregulatory intolerance similar to that observed following sustained exposure to a high fat diet. Since VMH glucoregulatory neurons are activated by physiological postprandial increase in local glucose level to increase peripheral insulin action, these VMH NA findings suggest a novel function of elevated VMH NA to block normal postprandial glucoregulatory sensing of VMH glucose excitatory (GE) neurons that potentiate postprandial insulin sensitivity. To test this postulate multi-barreled pipettes with carbon fiber recording electrodes were lowered into the VMH of anesthetized rats (N=10) (age 12 weeks, maintained on standard low fat rodent chow diet) and multi-unit responses (MURs) from the central recording electrode (~.5 MΩ) before and during glucose electro-osmotic injection into the VMH (to preferentially activate GE neurons) were obtained. Changes in MURs to such glucose administration (that were at least 15% above baseline, P<0.05) were compared when such glucose was co-administered with micro-injection periventricular and such NE treatment significantly and consistently reduced such glucose-induced MURs by 46% (P<0.05). Among those glucose-induced MURs greater than 100% above baseline, this NE inhibition was even greater (50%, P<0.05). These findings are the first to identify a novel role for increased VMH NA in the blockade of normal postprandial VMH glucoregulatory sensing that is involved in subsequent post-meal peripheral insulin action.

1806-P Glucagon Regulates Energy Balance via FGF-21 Signaling in the Brain SHELBY NASON, TEAYOUN KIM, JESSICA P. ANTIPENKO, JODI PAUL, BRIAN ROCHESTER, INDIANAPOLIS, IN

Glucagon is an essential regulator of glucose and lipid metabolism that also promotes weight loss. Thus, novel therapeutics that stimulate glucagon receptor (GcgR) signaling are promising for treatment of obesity and diabetes; however, the mechanism(s) underlying these effects are yet to be fully elucidated. We previously identified that hepatic glucagon signaling increases the secretion of another fasting hormone, Fibroblast Growth Factor (FGF) 21 (FGF-21), also known to be involved in regulating energy balance. We have recently observed that mice deficient for liver FGF-21 (FGF-21ΔmRNA) are partially resistant to the anti-obesity effects of GcgR agonism, clearly implicating hepatic FGF-21 as an essential component of the glucagon’s weight-loss effects. FGF-21 signals through an obligate co-receptor (γKlotho, Klb).

with expression limited to adipose tissue, liver, and brain, specifically within the suprachiasmatic nucleus (SCN) of the hypothalamus and the hindbrain. As the hypothalamus has known roles in regulating energy balance, we hypothesized that the anti-obesity action of the glucagon-FGF-21 system signals through a central mechanism. Mice deficient for neuronal Klb (KlbΔmRNA) are less susceptible to diet-induced obesity than wild type mice (P<0.01), with no observed differences in food intake or energy expenditure. Following chronic GcgR activation via the selective agonist IUB288, KlbΔmRNA mice exhibit a partial reduction in body weight (12%) in comparison to control mice (15%), suggesting that FGF-21 mediates glucagon’s anti-obesity properties through central action. Consistent with GcgR-stimulated, neuronal FGF-21 signaling, we found that neuronal activation, measured via immunochemistry, was increased in the SCN following IUB288 injection. Together, these data suggest that glucagon mediates part of its anti-obesity properties through FGF-21 KLB signaling in the SCN, and has implications for future treatments against obesity and the metabolic syndrome.

Supported By: National Institutes of Health

A480

1807-P Amygdala Glucose-Sensing Neurons Regulate Glucose Metabolism KAYVA DEVARAKONDA, MITCHELL BAYNE, ALEXANDRA ALVARSSON, SARAH STANLEY, New York, NY

Dysfunction of blood glucose produces health problems with profound consequences. In humans, the central nervous system (CNS) plays a vital role in glucose metabolism. The amygdala and basomedial amygdalar nuclei contain neurons that alter their firing in response to physiological changes in glucose concentrations and express glucokinase (GK), an enzyme thought to act as a glucose sensor in the CNS. However, little is known about the anatomy and function of these neurons. We have found that amygdala neurons express c-fos, a marker of neuronal activation, in response to changes in blood glucose. Using a transgenic mouse with Cre recombinase expression in GK neurons and the retrograde tracer pseudorabies virus (PRV), we have also found that GK-expressing neurons in the amygdala are part of a polysynaptic circuit to peripheral endocrine organs. Finally, modulating the activity of amygdala neurons alters both feeding and glucose metabolism. Together, these data support a role for amygdala glucose-sensing neurons in the regulation of glucose metabolism and behaviors that restore circulating glucose levels to normal.

Supported By: American Diabetes Association/Pathway to Stop Diabetes (117-ACE-91 to S.S.), Swedish Society for Medical Research, National Institutes of Health; Einstein-Mt. Sinai Diabetes Research Center, Alexandria and Alexander L. Sirinshneider Fund

INTEGRATED PHYSIOLOGY—INSULIN SECRETION IN VIVO

Moderated Poster Discussion: Integrated Physiology of Insulin Secretion In Vivo (Posters: 1808-P to 1813-P), see page 18.

1808-P Elevated Glucose Concentrations 60 Minutes After an Oral Challenge in Subjects with Normal Glucose Tolerance Are Not Explained by the Rate of Meal-Derived Glucose Appearance J.D. ADAMS, SERGEI TREIBER, MARIA D. HURTAADO, MARCELLO C. LAURENTI, CHIARA DALLA MAN, CLAUDIO COBELLI, ROBERT A. RIZZA, ADRIAN VELLA, Rochester, MN, Graz, Austria, Alzburgo, Italy, Padova, Italy

Glucose concentrations 60 minutes after an oral glucose tolerance test (OGTT) ≥155 mg/dl (8.6 mmol/L) identify an increased risk of progression to type 2 diabetes even in those with normal glucose tolerance (NGT). Recent data suggests that these differences can be explained by increased intestinal glucose absorption due to increased expression of the sodium/glucose cotransporter 1 (SGLT1) in the intestine. To examine the contribution of meal appearance to postprandial glucose concentrations we studied 36 subjects with NGT using a 75g OGTT, and a labelled mixed meal. Insulin secretion and action, endogenous glucose production (EGP), meal-derived glucose appearance (Meal Ra) and glucose disappearance (Rd) were subsequently calculated. Participants were grouped according to 60 minute glucose appearance (Meal Ra) and glucose disappearance (Rd) ≥155 mg/dl) or LO (<155mg/dl). No differences in age (47±3 years), BMI (30±2 kg/m2), family history of diabetes (10%), smoking status (20%), physical activity (12%), or body composition (fat 37.4±0.1% body fat, lean mass 63±1% lm, 27±1% fat mass after 8 weeks of HFD feeding; p<0.05). Together, these data suggest that neuronal mIndy is a critical regulator of energy and glucose homeostasis in mammals. Further studies will address the mechanisms involved in the effect.
lary peak (86±10 vs. 92±6 pmol/kg/min, p=0.59) and integrated (8.8±1.3 vs. 10.6±1.1 nmol per 6 h, p=0.69) Meal Ra did not differ between groups. On the other hand, when β-cell responsivity (Φ) was expressed as a function of insulin action (S), the resultingDisposition Index (DI) was lower in the HI group (1862±409 vs. 893±109 10⁻⁶ dL/kg/min per pmol/l, p=0.01). When analyzed as a continuous variable, 60 min related to DI (r = -0.37, p=0.02) but did not correlate with peak (r=0.03, p=0.96) and integrated (r=0.02, p=0.91)Meal Ra. Taken together, these data indicate that increased 80 minute glucose concentrations, even in subjects with NGT, are explained by decreased β-cell function not by an increased systemic rate of appearance of meal-derived glucose.

Supported By: National Institutes of Health R01DK78846, R01DK116231)

Does the Shape of the OGTT Glucose Curve Reflect Metabolic Function in Individuals with Type 2 Diabetes? Baseline Data from the GRADE Cohort

KIRSTINA UTTSCHEIDNER, MARY ANN BANERJI, JOSHDIA J. BARZILAY, ERIC V. GONZALEZ, FARAMARZ ISMAIL-BEISI, KIEREN J. MATHER, PHILIP RASKIN, NAJII YOUNES, STEVEN E. KAHN, GRADE RESEARCH GROUP, Seattle, WA, Brooklyn, NY, Duluth, GA, Houston, TX, Shaker Heights, OH, Indianapolis, IN, Dallas, TX, Rockville, MD, Washington, DC

In nondiabetic subjects a biphasic (rise, fall, rise) vs. monophasic (rise then fall) glucose pattern on OGTTs has been associated with better metabolic parameters, but data in T2DM are limited. We categorized the shape of the glucose curve from baseline OGTTs performed in the Glycemia Reduction Approaches in Diabetes Study (GRADE) into monophasic, biphasic or continuous rise and analyzed their relationship with metabolic parameters. GRADE eligibility included T2DM <10 y, HbA1c 6.8-8.5% with metformin treatment alone. OGTT glucose and insulin were measured at 0, 15, 30, 60, 90 and 120 minutes (n=5047 adults: age 57±10 y, 83.6% male, HbA1c 7.5±0.5%, duration T2DM 4.2±2.8 y). Most glucose profiles were monophasic. HbA1c did not differ between groups. Those with a monophasic shape were more likely to be men, had higher BMI, fasting glucose and inAUC glucose, and lower HOMA-S and disposition index (Table). Compared to the monophasic group, those with a continuous rise shape had lower fasting glucose and higher HOMA-S, but the highest 2 h glucose. Those with a biphasic pattern had intermediate insulin sensitivity, but the highest disposition index. Thus, a biphasic glucose pattern reflects better β-cell function, similar to that observed in nondiabetic subjects. Whether glucose patterns predict response to GRADE interventions will be determined on study completion.

Table. Phenotypic and Metabolic Characteristics by OGTT Glucose Curve Shape.

<table>
<thead>
<tr>
<th></th>
<th>Monophasic</th>
<th>Biphasic</th>
<th>Continuous</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>322(64.0)</td>
<td>283(56.0)</td>
<td>152(30.4)</td>
<td></td>
</tr>
<tr>
<td>Sex (%male)</td>
<td>70.3</td>
<td>59.7</td>
<td>50.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32±7</td>
<td>32±6</td>
<td>32±7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.5±0.5</td>
<td>7.5±0.5</td>
<td>7.5±0.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>8.3±1.7</td>
<td>8.4±1.8</td>
<td>8.3±1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2 hour glucose (mmol/l)</td>
<td>15.4±2.9</td>
<td>15.8±3.1</td>
<td>17.1±3.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>incrementalAUC₁₈₀ (mmol/l)</td>
<td>6.4±1.5</td>
<td>5.3±1.7</td>
<td>5.1±1.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA-S (mIU/mmol/l)</td>
<td>0.22±0.23</td>
<td>0.25±0.21</td>
<td>0.28±0.41</td>
<td>0.01</td>
</tr>
<tr>
<td>AUCinsulin (mIU/ml)</td>
<td>5.3±4.4</td>
<td>6.3±5.8</td>
<td>5.1±6.1</td>
<td>0.002</td>
</tr>
<tr>
<td>Disposition index (mIU/l)</td>
<td>0.3±0.06</td>
<td>0.4±0.43</td>
<td>0.3±0.37</td>
<td>0.005</td>
</tr>
</tbody>
</table>
| Mean±SD. 23 had missing data and 8 were excluded with a triphasic pattern. Disposition index = AUCΔG₀₋₁₈₀/HOMA-S.

Supported By: National Institute of Diabetes and Digestive and Kidney Diseases

The Relationship of Fasting Free Fatty Acids, Adipose Tissue, Insulin Resistance, and Fasting Glucose Concentrations with Subsequent β-Cell Function in Nondiabetic Subjects

MARIA D. HURTAZCO, J.D. ADAMS, MARCELLO C. LAURENTI, CHIARA DALLA MAN, CLAUDIO COBELL, ROBERT A. RIZZA, MICHAEL D. JENSEN, ADRIAN VELLA, Rochester, MN; Albuzarni, Italy; Padova, Italy

Elevations in both plasma free fatty acids (FFA) and glucose concentrations during fasting are associated with impaired β-cell function and prediction from prediabetes to diabetes. Their interaction and subsequent effect on β-cell function as quantified by Disposition Index (DI) is unknown. We therefore measured total, saturated, mono-unsaturated and poly-unsaturated FFA concentrations using LC/MS in 120 nondiabetic subjects (cross-sectional subjects had increased β-cell function. When BMI, insulin resistance and HOMA-S were adjusted for covariates, the β-coefficient remained statistically significant. In summary, we have shown that continuous OGTT glucose shape is related to metabolic parameters, β-cell function and predicted response to GRADE treatments.
Integrated Physiology—Insulin Secretion in Vivo

1813-P
Altering Glucose Variability with Low- or High-Glycemic-Index Diets in Adults with Prediabetes Does Not Affect Beta-Cell Function or Markers of Oxidative Stress
KRISTINA UTSCHNEIDER, TONYA N. JOHNSON, KARA BREYMEYER, MARIAN L. NEUHOUSER, Seattle, WA

High glycemic variability has been associated with increased oxidative stress and β-cell dysfunction. To test whether changes in glycemic variability impact β-cell function and oxidative stress markers in adults with prediabetes, we conducted an RCT where we provided subjects controlled diets varying in glycemic index (GI) to experimentally manipulate post-prandial glucose excursions. After 2 weeks on a control diet (mean GI = 55±8), subjects were randomized to 1 of 3 groups for 4 weeks: low-GI (<35) GI diet, high (HGI) (>70) GI diet plus placebo (HGI/PLAC), or subjects underwent CGMS (ipro), fasting markers of oxidative stress (GSH/GSSG and TBARS) and a 180 min OGTT at the end of each diet. Independent t-test was used to test the intervention effect on the change in disposition index (DI), a marker of β-cell function. Fifty-two subjects (29M/26F, age 53.1±10.3 years, BMI 32.1±6.2 kg/m²) with IFG and/or IGT completed the study (18 LGI, 17 HGI/NAC, 17 HGI/PLAC). The 3 groups did not differ by sex, age, BMI, A1c, fasting or 2 h glucose (ANOVA). On the control diet, DI was inversely correlated with CGMS mean daily glucose (r = -0.32, p = 0.02) and daily SD glucose (r = -0.31, p = 0.03) and the GSH/GSSG ratio (r = -0.35, p = 0.01), but not TBARS (r = 0.13, p = 0.54). Compared to LGI, HGI/PLAC increased mean CGMS glucose (change-1.4±1.9, LGI vs. 4.2±4.6; HGI/PLAC vs. 0.05±0.05) and SD (change-2.6±1.3 vs. 5.0±2.2, p = 0.056). Results did not differ between HGI/PLAC and HGI/NAC. There were no significant intervention effects on DI, TBARS or GSH/GSSG ratio. Changes in CGMS mean glucose and SD and oxidative stress markers did not correlate with changes in DI.

In conclusion, GI diet-induced changes in glucose concentrations and variability did not impact β-cell function or oxidative stress markers. These results suggest that glucose variability may be a consequence of β-cell dysfunction rather than a cause.

Supported By: National Institutes of Health; U.S. Department of Veterans Affairs

1815-P
Treatment of Hyperglycemia with Empagliflozin, With or Without Metformin, Improves Islet Endothelial Cell Health and Insulin Secretion in db/db Diabetic Mice
MEGHAN F. HOGAN, DARYL J. HACKNEY, ALFRED AFLUN, THOMAS D. MUNDINGER, SAKENEH ZRAIKA, REBECCA L. HULL, Seattle, WA

Islet endothelial dysfunction occurs in diabetic mice and results in impaired insulin release in vitro. Previously, we found that 12-week treatment of db/db mice with the SGLT2 inhibitor empagliflozin (EMPA) improved islet endothelial dysfunction. Here, we determined if this occurs with shorter treatment duration, is associated with increased insulin release and whether EMPA combined with metformin (MET) provides additional benefit. 6-week old male diabetic C57BL/KsJ-db/db mice and littermate controls (db/c/+4) were treated with EMPA (20 mg/kg/d in diet), MET (0.5 g/kg/d in water), EMPA+MET, or vehicle (VEH) for 8 weeks. A subset of mice (n=3-5) underwent IV glucose tolerance tests to determine insulin release. mRNA levels of cell adhesion molecules E-selectin (Selecte) and vascular cell adhesion molecule 1 (Vcam1), proinflammatory cytokine interleukin-6 (Il6) and vasoconstrictor endothelin-1 (Edn1), were assessed. EMPA treatment lowered plasma glucose, increased insulin release and improved islet endothelial health (Table). MET had a similar effect, but was less effective than EMPA, while EMPA+MET was more effective in improving endothelial function but did not further increase insulin release. Improving islet endothelial health with EMPA may have beneficial effects on beta-cell function in human type 2 diabetes.

Table.

Supported By: National Institutes of Health; Boehringer Ingelheim

A482

1814-P
The Role of Incretins and Insulin Clearance in Postprandial Hyperinsulinemia in Black Women—The Federal Women Study
STEPHANIE T. CHUNG, AMANDA D. COURVILLE, PAOLA C. ALDANA, ANTHONY L. NEUHOUSER, Seattle, WA

In this study, we examined whether the elevation in FFA reflects defects in production or uptake, and whether fasting FFA concentrations could modulate by fasting FFA concentrations. These differences were no longer apparent within 80 minutes of OGTT and all groups suppressed FFA to the same nadir (166 ± 12 vs. 174 ± 14 µmol/L, p = 0.59). On the other hand, an inverse relationship (r = -0.02) of fasting FFA (r = -0.33) and of Adipo-IR (r = -0.28) was observed with insulin action (Si). Fasting FFA did not correlate with β-cell responsivity (Φ Φ), r = 0.04). However, higher Adipo-IR was associated with higher values of Φ Φ (r = -0.36, p < 0.01). Fasting glucose concentrations did not alter these relationships; specifically no interaction of glucose with FFA during the fasting state to influence DI was evident. It remains to be ascertained whether the elevation in FFA reflects defects in production or in uptake, and whether the effect of changes in fasting glucose concentrations on DI is modulated by fasting FFA concentrations.

Supported By: National Institutes of Health
mined. Study design included 4 groups: T1D patients < 1 year of diagnosis; AAB+ first-degree relatives (FDR); AAB- FDR, and AAB- controls. Fasting subjects underwent pancreatic magnetic resonance imaging (MRI) and images were analyzed by radiologists blinded to group. Relative PV (RPV=PV/BMI) was analyzed utilizing a linear mixed model accounting for age, gender, and family clustering with Tukey correction for multiple comparisons. A total of 223 subjects were enrolled with overall age of 19.6±10.5 years (45% males). RPV was significantly higher in controls (n=49) than AAB- FDR (n=80), AAB+ FDR (n=62, single AAB+ n=30, multiple AAB+ n=32) and recent onset T1D (n=52) (Figure). RPV was also significantly higher in AAB- FDR and AAB+ FDR vs. recent onset T1D (Figure). 1. Pancreas MRI demonstrates smaller RPV in AAB- FDR than age-matched controls and patients with recent onset T1D have lower RPV than those FDR with established autoimmunity. Pancreas MRI may improve our understanding of the natural history of T1D.

Figure 1.

Supported By: National Institutes of Health (DP3 DK101120)

PBI-4547 Prevents Progression of Prediabetic Condition to Type 1 Diabetes in NOD Mice
FRANCOIS A. LEBLOND, KATHY HINCE, FRANCOIS SARRA-BOURNET, WILLIAM GAGNON, MIKAEL TREMBLAY, MARIE-FIER CLOUTIER, SYLVIE LETOURNEAU, JEAN-CHRISTOPHE SIMARD, MARTIN LEDUC, BRIGITTE GROUX, PIERRE LAUWIN, LYNE GAGNON, LaRocque, Canada

Introduction: PBI-4547 is a novel orally active compound that is being developed for potential clinical use in patients suffering from metabolic and inflammatory/fibrosis-related diseases. This study examined the effect of PBI-4547 in NOD mice, a model of type 1 diabetes. Our objective was to demonstrate the efficacy of PBI-4547 to stop the progression of diabetes in mice exhibiting prediabetic glucose escalation.

Methods: NOD/ShiLtJ female mice (8 weeks of age) were followed up to the appearance of the first sign of hyperglycemia (three consecutive weeks of glucose increase >7 mmol/l). Once identified as prediabetic, mice were randomly allocated to control (receiving vehicle (water)) or PBI-4547 (25 mg/kg/day) groups for treatment by daily gastric gavage for 8 to 12 weeks.

Results: Mice treated with vehicle (n=9) evolved to a moderate to severe diabetic condition (glucose levels >11.7-37 mmol/l). Most of these vehicle-treated mice (8/9) survived only a few weeks after the onset of the prediabetic condition. At the opposite, NOD mice treated with PBI-4547 all showed a reversal of their hyperglycemia and none of the observed animals (n=12) evolved to a chronic hyperglycemia (>11 mmol/l). Survival was also significantly improved in the group treated with PBI-4547 with 8 of 12 mice surviving more than 10 weeks after the onset of treatment. Analysis of insulinemia showed a significant difference between both groups. Immunohistological analysis of pancreas recovered at euthanasia revealed a significant reduction in islet inflammatory cell infiltration. Moreover, NOD mice treated with PBI-4547 maintained normoglycemia despite a reduced number of islets. In fact, PBI-4547 reduced by 30% the number of severely damaged islets.

Conclusions: These data suggest that PBI-4547 could preclude the evolution of diabetes in a type 1 model.

ADA-Supported Research
Moderated Poster Discussion

1818-P
Normal Glucose Tolerance (NGT) in Obese African-Americans (AA) with Ketosis-Prone Diabetes (KPDM)
PRIYATHAMA VELLANKI, DARKO STEFANOVSKI, VISHAL NARWANI, ISABEL ANZOLA, LIMIN FENG, DAWN SMILEY-BYRD, GUILLERMO E. UMPRIEREZ, Atlanta, GA, Philadelphia, PA

KPDM is characterized by new-onset DKA and near-normoglycemia remission (HbA1c < 7%, fasting blood glucose [BG] < 130 mg/dl, and maintain glycemic control for at least one week off insulin) with intensive insulin treatment. Glycemic status at insulin remission varies from NGT, prediabetes or diabetes on OGTT. We hypothesized that patients with NGT at near-normoglycemia remission will have higher insulin sensitivity (S) and secretion and longer hyperglycemia relapse-free survival. Obese AA who presented with DKA (n=53) and severe hyperglycemia (n=42) [BG > 400 mg/dl with no DKA] underwent 2 hour 75gm OGTT a week after insulin remission. NGT, prediabetes and diabetes were defined as per ADA criteria. At near-normoglycemia remission, S was calculated using the OGTT minimal model analysis. Insulin secretion was calculated as incremental area under the curve of insulin (IncreAUC) with insulin levels from OGTT. Disposition index (DI) was calculated as S x IncreAUC. Hyperglycemia remission was defined as fasting BG > 130 mg/dl, HbA1c < 7% or 2 random BG > 180 mg/dl. There were no differences in baseline characteristics among patients with NGT (12%), prediabetes (45%) and diabetes (43%). DI was higher in patients with NGT vs. prediabetes vs. diabetes (1.88±1.63 vs. 1.05±1.14 vs. 0.35±0.92, p<0.001). The difference in DI was explained by higher S, than IncreAUC, in NGT compared to prediabetes and diabetes (5.4±2.4x vs. 2.4±3.5 vs. 1.2±2.5 10^-4 (mU/l)^2/min), p<0.001; IncreAUC; 657±13451 vs. 6585±4947 vs. 4450±3051, p=0.14 mU/l/min). Multivariate Cox regression showed that age, sex, DKA presentation, OGTT status, and DI were not associated with long-term relapse-free survival. There were no differences in any variables between patients presenting with DKA or severe hyperglycemia. NGT at near-normoglycemia remission is characterized by higher insulin sensitivity than higher insulin secretion. However, none of these markers were associated with long-term hyperglycemia-free survival.

Supported By: National Institutes of Health (K12/DK08580, K08/DK083061)

1819-P
Association of Pancreas Fat with Impaired Insulin Secretion Depends on Liver Fat and Circulating Fatty Acids
BENJAMIN JAGHOURZ, ROBERT WAGNER, JÖRGEN MACHANN, NÖRBERT STEFAN, ANDREAS PETER, DOROTHÉA 1, SIEGEL-AXEL, FELICIA GERST, SUSANNE ULLRICH, ANDREAS FRITSCHE, HANS-ULRICH HAERING, MARTIN HENI, Tübingen, Germany

Objective: Beta cell failure is a crucial factor in the pathogenesis of type 2 diabetes. Fat accumulation within the pancreas is associated with impaired insulin secretion only in the context of prediabetes. In vitro evidence suggests an underlying mechanism that depends on the crosstalk between fatty liver and pancreatic fat via circulating factors, including free fatty acids. We now addressed the existence of such an inter-organ crosstalk in humans. We therefore tested for interaction between pancreatic fat content, liver fat, and circulating free fatty acids on insulin secretion.

Methods: We metabolically characterized 296 individuals (93 males/203 females) at increased risk of type 2 diabetes by an 75g oral glucose tolerance test. Insulin sensitivity, insulin secretion, and free fatty acid levels were assessed. Pancreatic fat accumulation was measured by MR-imaging, liver fat was determined by MR-spectroscopy.

Results: There was a significant interaction between pancreatic fat content, liver fat, and free fatty acids on insulin secretion (e.g., p < 0.03 for insulinogenic index). Pancreatic fat was negatively associated with insulin secretion when liver fat content and levels of free fatty acids were markedly elevated. In contrast, at median liver fat and free fatty acid levels, no such relation was detectable.

Conclusion: Pancreatic fat accumulation appears to be harmful for human beta cell function only when additional factors, i.e., fatty liver and elevated levels of circulating free fatty acids are present. These results can explain why the impact of pancreas fat on insulin secretion is only detectable in a prediabetic context and point towards liver fat and circulating factors as possible targets to indirectly improve beta cell function.

Supported By: Deutsches Zentrum für Diabetes Forschung

1817-P
Depends on Liver Fat and Circulating Fatty Acids
Supported By: National Institutes of Health (DP3 DK101120)

Association of Pancreas Fat with Impaired Insulin Secretion

Supported By: Deutsches Zentrum für Diabetes Forschung
**1820-P**

**Effects of GLP-1 and GIP on Insulin Secretion in Glucose Intolerant, Pancreatic Insufficient Cystic Fibrosis**

JACK N. EIEL, SARAHR NYRIJESY, AMY J. FELECKIS, DIVA DE LEON, DENIS HAULIJADIS, CHRISTINA KUBRACK, ABIGAIL TAM, SABA SHEIKH, RONALD C. RUBENSTEIN, ANDREA KELLEY, MICHAEL R. RICKELS, Philadelphia, PA

Individuals with pancreatic insufficient cystic fibrosis (PI-CF) and glucose intolerance demonstrate impaired incretin and insulin secretion. The goal of this study was to assess β-cell responsiveness to the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) during glucose potentiated arginine (GPA) testing in adults with PI-CF and abnormal glucose tolerance. Participants were randomized to receive either GLP-1 (n=15) or GIP (n=15) and then underwent GPA testing during either incretin or placebo infusion in a randomized, cross-over fashion. Glucose was similar between groups (fhr: 214±8 vs. 206±7 mg/dL, 2hr: 141±18 vs. 150±18 mg/dL). During GPA-1 infusion, fasting glucose was lower after 30 min vs. placebo (p<0.001), and during the 230 mg/dL glucose clamp the glucose infusion rate (GIR) was higher (p<0.001). Second phase insulin levels were substantially increased prior to arginine administration under 230 mg/dL clamp conditions vs. placebo (p<0.001), but no difference in the acute insulin response (AIR) to GPA was present. At 230 mg/dL, proinsulin and C-peptide were increased under GLP-1 vs. placebo (both p<0.001), but the proinsulin secretory ratio (PISR) was unchanged. During GIP infusion, fasting glucose was slightly lower after 30 min vs. placebo (p<0.05), but no difference in the GIR required to achieve 230 mg/dL was found. Second phase insulin levels were not different during the 230 mg/dL glucose clamp. The AIR to GIP was lower during GPA vs. placebo (p<0.01). Second phase proinsulin and C-peptide levels were higher with GIP vs. placebo (both p<0.01) with an increased PISR (p<0.05). These results indicate that GLP-1 augments glucose-dependent insulin secretion while GIP may lead to disproportionate proinsulin secretion in glucose intolerant PI-CF. Further studies should determine whether GLP-1 may provide a therapeutic benefit in this population.

Supported By: National Institutes of Health (RO1DK093930, K23DK097937, U11TR000033, PO3DK099255, T32DK07314)

---

**1822-P**

**Relationship between Baseline Phenotype and Measures of Insulin Sensitivity and Beta-Cell Responses in the GRADE Cohort**

NEDA RASDOLI, RObERT M. COHEN, RALPH A. DEFRONZo, SILVIO INZUCCHI, FARRAMARZ ISMAIL-BEGI, STEVEN E. KAHN, KRISTINA UTSCHNIEDER, JOHN LACHIN, NAJY YOUNES, GRADE RESEARCH GROUP, Denver, CO; Cincinnati, OH; San Antonio, TX; New Haven, CT; Shaker Heights, OH; Seattle, WA, Rockville, MD; Washington, DC

Factors associated with β-cell dysfunction in type 2 diabetes (T2D) are not well understood. We examined the association between OGTT-derived estimates of insulin sensitivity, insulin/C-peptide responses and β-cell function with baseline phenotypic characteristics in the GRADE cohort. The cohort comprised 5,447 adults with T2D <10 y, treated with metformin alone. Subjects were 62.6% men, 57.2±10 years old (mean±SD), with BMI 34.3±6.8 kg/m2, weight 99.8±22.3 kg, waist circumference (c) 112.3±15.6 cm, HbA1c 7.5±0.5% and T2D duration 4.2±2.6 y. Racial composition was 86% white, 20% African Americans, 4% Asian, 3% American Indian, and 7% other. Insulin sensitivity did not differ between men and women, but women had higher insulin/C-peptide responses and disposition index (DI) (p<0.001 for all). The associations between insulin sensitivity, insulin/C-peptide responses and DI with age, BMI, weight, waist circumference and T2D duration are provided in Table 1. Insulin sensitivity, insulin/C-peptide responses and DI differed by racial category (p<0.001 for all).

In summary, among GRADE participants, sex, race and obesity are associated with β-cell function. Although statistically significant, the associations of insulin sensitivity and β-cell responses with age and T2D duration are not as strong.

Table 1. The Spearman Correlation (Upper Line) and p Value (Lower Line) between Baseline Phenotypic Characteristics and Insulin Sensitivity, Insulin/C-Peptide Responses and DI

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Age</th>
<th>Weight</th>
<th>BMI</th>
<th>Waist Circ</th>
<th>T2D Duration</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matsumura Index</td>
<td>0.07</td>
<td>0.41</td>
<td>0.08</td>
<td>0.06</td>
<td>0.06</td>
<td>0.08</td>
</tr>
<tr>
<td>HOMA-S Index</td>
<td>0.12</td>
<td>0.47</td>
<td>0.13</td>
<td>0.19</td>
<td>0.09</td>
<td>0.06</td>
</tr>
<tr>
<td>Insulin response</td>
<td>0.04</td>
<td>0.26</td>
<td>0.02</td>
<td>0.19</td>
<td>0.08</td>
<td>0.06</td>
</tr>
<tr>
<td>C-peptide response</td>
<td>0.07</td>
<td>0.14</td>
<td>0.03</td>
<td>0.15</td>
<td>0.09</td>
<td>0.01</td>
</tr>
<tr>
<td>Disposition Index</td>
<td>0.11</td>
<td>0.13</td>
<td>0.11</td>
<td>0.12</td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>Insulin response (0-30)/Glucose (0-30)</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>C-peptide response (0-30)/Glucose (0-30)</td>
<td>0.07</td>
<td>0.15</td>
<td>0.02</td>
<td>0.12</td>
<td>0.08</td>
<td>0.01</td>
</tr>
<tr>
<td>p Value</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Supported By: National Institute of Diabetes and Digestive and Kidney Diseases

---

**1823-P**

**Beta-Cell Function after Gastric Bypass**

ANKIT SHAIK, KARRA LEESQUE, MICHAEL AITERS, MARLENA M. HOLTZ, FATIMA ALAM, ESPERIDIA PERINI, BETSY L. ROJAS, VICTORIA MARK, KAPILA PATEL, ROXANNE DUTIA, EUGENIUS J. HARVEY, KOJI PARK, NINAN KOSHY, SCOTT J. BELSLEY, JAMES J. MCGINTY, BLANDINE LAFERRERE, New York, NY

β-cell glucose sensitivity (BCGS) improves after gastric bypass (RYGB) in individuals with diabetes (DM2) remission. We sought to assess BCS (pmol/kg/min/mM) after an oral glucose test (OGT) and an IV graded glucose infusion (GGI) in subjects with and without DM2 remission after RYGB. Twenty-five subjects with DM2 were studied with GGI and 75g-OGT before and 3 months after RYGB. Glucose, insulin, C-peptide, insulin secretion rate, GLP-1 and BCS were assessed during the OGT and the GGI. Data are presented as means/SD. Within and between group comparisons with paired and unpaired t-test; GLM with repeated measure to assess change before and 3 months after RYGB. Of the 25 subjects studied presurgery, 10 experienced DM2 remission (REM), 9 remained with DM2 (N-REM) at 3 months; 6 remained glucose intolerant and were not included in the analysis. Pre-surgery BMI (41.5±4.7 kg/m2), weight (108.3±15.9 kg), age (43.8±8.8 years), gender (95% female), HOMA-IR (12.1±6.7) and Matsumuda index did not differ between groups; N-REM had longer DMZ duration (14 vs. 2.5 y p=0.001), higher HbA1c (6.2±1.0 vs. 7.8±0.9%, p=0.01) and more likely to be taking insulin (7/9 vs. 0/10 p=0.01). Prior to RYGB, OGT-BCGS was 4x greater (0.83±0.60 vs. 0.22±0.24, p=0.01) and GGI-BCGS was 2.5x greater (0.48±0.30 vs. 0.19±0.15, p=0.04) in REM vs. N-REM. Weight loss did not differ for REM and N-REM (17±5%). HOMA-IR, GLP-1 and GGI-BCGS improved similarly in both groups. OGT-BCGS increased in both groups, but more in REM vs. N-REM (+1.31±1.0 vs. +0.30±0.28, p=0.01). The difference between OGT-BCGS and GGI-BCGS observed pre-RYGB.

Supported By: Competence Centers for Excellent Technologies
(0.58±0.54 vs. 0.38±0.35, p<0.05) was exaggerated at 3 months by 4x in REM (2.13±1.08 vs. 0.58±0.15, p<0.001) and −2.5x in N-REM (0.6±0.43 vs. 0.24±0.17, p=0.07).

In conclusion, β-cell function assessed during an IV GGI improves by the same magnitude regardless of DM2 remission status after RYGB. However, β-cell function improved more in REM than N-REM after oral glucose, suggesting a greater incretin effect, or other gut-related mechanisms, in REM after RYGB.

Supported By: National Institutes of Health (R01DK-098056-03, UL1TR001873, F32DK113747-01A1)

**1824-P**

**Beta-cell SCHAD Deficiency Causes Hyperglycemia in Mice**

JOHANNA LUEDEKE, KELLY M. VELASCO, DARIO F. DE JESUS, BRITTANY A. SLIPP, JIANG HU, SOLRUN J. STEINE, GEIR HELGELAND, PÅL RASMUS NJØLSTAD, RÖGHT KULKARMI, ANDERS MOLVESEN, Bergen, Norway; Boston, MA; Liege, Norway.

Congenital Hyperinsulinism of Infancy (CHI) is a group of rare, inherited disorders with persistent hyperglycemia due to hyperinsulinemia. CHI is caused by mutations in genes that affect regulation of insulin secretion in β-cells. One such gene is HADH, which encodes short-chain 3-hydroxyacyl-CoA dehydrogenase (SCHAD), a metabolic enzyme of the fatty acid beta-oxidation pathway. Mutations resulting in SCHAD deficiency cause protein-sensitive CHI and increased systemic levels of some fatty acid oxidation metabolites.

To test the hypothesis that SCHAD-CHI is caused by a specific deficiency of this ubiquitously expressed protein in β-cells we created β-cell-specific SCHAD knock-out (β-SCHADKO) mice by crossing Hadd-flxed animals with mice expressing Cre under the regulation of the Ins1 promoter. Validity of the β-SCHADKO model was confirmed by PCR, Western Blot and immunofluorescence staining of pancreas tissue. Growth and development of β-SCHADKO mice was similar to littermate controls. Plasma glucose in the KOx was significantly reduced in the random fed state (♀: 82±15 vs. 115±28 mg/dL, p=0.001; ♂: 143±8 vs. 179±19 mg/dL, p<0.001) and after overnight fasting (♀: 82±14 vs. 156±23 mg/dL, p<0.002; ♂: 62±7 vs. 74±9 mg/dL, p<0.001). Insulin and C-peptide levels were elevated in female KOs after overnight fasting (insulin: 0.25±0.15 vs. 0.38±0.23 ng/mL, p=0.057; C-peptide: 0.15±0.07 vs. 0.26±0.16 ng/mL, p=0.05), but unchanged in the fed state. GSIS and overall glucose homeostasis, as assessed by insulin and glucose tolerance tests, were not significantly altered. Overall, these data indicate that the β-SCHADKO mouse is a suitable model to investigate the hypoglycemic phenotype of underlying SCHAD deficiency.

Supported By: Research Council of Norway

**1825-P**

**Pharmacological Neprilysin Inhibition Improves Glucose Homeostasis in a Mouse Model of Type 2 Diabetes**

JACQUELINE H. PARILLA, STEVE MONGOVIN, BREANNE BARROW, NATHALIE ESSE, SAKEREN ZHAIKA, Seattle, WA.

Neprilysin (NEP) is a ubiquitous peptidase whose plasma activity in humans and rodents increases in conditions associated with type 2 diabetes (T2D). In high fat-fed mice, increased plasma NEP activity correlates with insulin resistance and impaired β-cell function, and we’ve shown genetic ablation of NEP ameliorates these deleterious effects, thereby decreasing glucose levels. Thus, we sought to determine whether clinically relevant, pharmacological inhibition of NEP also confers beneficial effects on glycemic status in a mouse model of T2D. Five-week old C57BL/6 mice were fed high fat diet for 3 weeks, followed by injection of low-dose beta-cell toxin streptozotocin (30 mg/kg i.p. once daily for 3 consecutive days; STZ) to induce diabetes, or vehicle (VEH) as a control. Mice were continued on high fat diet alone (CON) or supplemented with the NEP inhibitor sacubitril (48 mg/kg/day; SAC) for 8 weeks. Body weight did not differ among the 3 groups of mice at baseline (Table), and increased to a similar extent in all groups after 8 weeks of treatment. Further, both fasting and fed glucose levels were similar in CON vs. VEH-CON mice after 8 weeks, but significantly lower in STZ-SAC vs. STZ-CON mice.

Together, these data show that pharmacological NEP inhibition improves both fasting and fed glucose levels in a mouse model of T2D, and thus may be a useful treatment strategy in human T2D.

**1826-P**

**Retinol Binding Protein 4 Impairs Pancreatic Beta-Cell Function, Leading to the Development of Type 2 Diabetes**

RONG HUANG, XINXIU BAI, XUEYAN LI, LINA ZHAO, MIN XIA, Guangzhou, China.

Circulating Retinol binding protein 4 (RBP4), the specific transport protein for vitamin A, has been implicated in insulin resistance and type 2 diabetes. Pancreatic beta cell failure plays a decisive role in the onset and the progression of type 2 diabetes. However, the effect of RBP4 on beta cell function and the molecular mechanisms are far from clear. The direct effect of RBP4 on insulin secretion was assessed by treating primary isolated islets from C57BL/6 mice with different dose of RBP4 (0.20, 40, 60 µg/ml) for 24 hour or with 60µg/ml RBP4 for different time points (0, 12, 24, 48 hours). We found that RBP4 could dose and time dependently inhibit the glucose stimulated insulin secretion (GSIS). To further identify the role of RBP4 on beta cell function, RBP4-overexpressing mice (RBP4-Tg) were generated. Compared to the wild type group, the islets isolated from RBP4-Tg mice showed a significant decrease of insulin secretion in response to glucose (~50%) and KCl (~70%). The Dynamic insulin secretion of the isolated islets of RBP4-tg mice in response to glucose was further characterized. RBP4 could dramatically inhibit first-phase GSIS by up to 80%. In consistent to these in vitro findings, RBP4-tg mice showed a progressive decrease of GSIS (~50%, 12, 16 weeks) which appeared as early as 8 weeks. While the glucose tolerance of these mice was not significantly impaired until 12 weeks by intraperitoneal glucose tolerance test and the insulin sensitivity was not changed until 16 weeks by intraperitoneal insulin tolerance test respectively.

In conclusion, RBP4 could impair pancreatic beta cell function which may lead to the onset and the development of T2DM.

**1827-P**

**Mild Physiologic Hyperglycemia Impairs Beta-Cell Function and Induces Insulin Resistance in Healthy Normal Glucose Tolerant Subjects**

AURÓRA MERÓVICI, ENRIQUE R. MALDONADO CORCHADO, DEVJIT TRIPATHY, RALPH A. DEFRONZO, San Antonio, TX.

The aim of the present study was to evaluate the effect of a physiologic increase (~45 mg/dl) in plasma glucose concentration on insulin secretion in healthy NGT individuals. 20 NGT subjects: 12 without family history of T2DM (FH-) (BM/3F, age = 50 ± 4 years, BMI = 27 ± 1 kg/m²) and 8 with FH (FH+) (4M/4F, Age = 48±2, BMI = 26±1) received an OGTT and 2-step hyperglycemic (~125 + 300 mg/dl) clamp (duration of each step = 80 minutes) followed by IV arginine (5g bolus). The acute insulin response (AIRi, min), 2h phase (SP) insulin secretion (IR) (SPS0−60 and SPS60−120 minutes during each hyperglycemic step and following arginine (AIRi,t) were assessed. Insulin sensitivity was assessed as the glucose infusion rate/steady state plasma insulin (M/I) during the hyperglycemic clamp. FPG concentration increased from 97±4 to 140±4 mg/dl for 48 hours by a variable IV glucose infusion. First phase insulin secretion (0-10 min) and 2h phase insulin secretion (10-80 and 90-60 min) increased by 59% and 78%, respectively, following chronic glucose infusion while insulin sensitivity (M/I) during both hyperglycemic clamp steps declined (15± 3.5 to 12±2.8 and 20.8 ± 4.7 to 8.1 ± 2.0, both p<0.02). Consequently, the insulin secretion (AIRi,t) and insulin resistance (disposition index) declined by 85± 18% (1h clamp step) and 81±45% (2h clamp step) (both p<0.05) following chronic glucose infusion. Similar changes were observed when indices of insulin secretion were measured using C-peptide. There was no difference in the effect of chronic glucose infusion on insulin secretion and insulin sensitivity between subjects with and without FH of T2DM. These results demonstrate that: (i) sustained physiologic hyperglycemia impairs insulin sensitivity (glucotoxicity); (ii) increases absolute insulin secretion; (iii) impairs beta cell function as measured with the disposition index (glucotoxicity).

Supported By: National Institutes of Health
1828-P

Metabolic Clearance Rate of Insulin Is Not Saturable within the Physiological Range
ISAAC ASARE BEDIako, REBECCA L. PASZKIEWICZ, ORISON O. WOOLCOTT, RICHARD N. BERGMAN, Los Angeles, CA

The plasma concentration of insulin is determined by pancreatic beta cell secretion and the metabolic clearance of the hormone. It has been suggested that the concentration of insulin determines its metabolic clearance rate. Also, some reports suggest that clearance is saturable and insulin kinetics are non-linear even within physiologic ranges. We assessed the metabolic clearance rate of insulin at different physiologic concentrations to access if clearance changes with concentration. Using the dog model (n=12), insulin was infused peripherally at 3 incremental rates (dose-response) during the euglycemic clamp. Each infusion rate spanned 90mins, and the last 30mins was considered the steady state. The metabolic clearance rate of insulin was calculated as the ratio of the infusion rate to the steady state plasma concentration. The 3 infusion rates, 1.5, 3.0 and 4.5 pmol/kg/min yielded steady state plasma insulin concentrations of 92 ± 8, 165 ± 12 and 256 ± 18pm respectively. The metabolic clearance rate of insulin was consistent and independent of dose (17.8 ± 1.7, 19.1 ± 1.2 and 16.6 ± 1.4 ml/kg/min; p = ns) across the different plasma insulin infusion rates. Also, we found a strong linear correlation (r = 0.99) between the infusion rates and steady state insulnin concentrations. Insulin kinetics are linear and the metabolic clearance of insulin is not saturable within physiologic ranges in the conscious dog. Though it’s possible that the site of degradation (i.e., liver vs. periphery) may change with dose. These data demonstrate that changing concentrations of plasma insulin within physiologic concentrations does not change the rate of insulin removal from the plasma.

Supported By: National Institutes of Health

1829-P

Sodium-Glucose Cotransporter 2 Inhibitors Improve Pancreatic β-Cell Function by the Relief of β-Cell Distress in Japanese Type 2 Diabetes
TSUNEHIKO YAMAMOTO, Amagasaki, Japan

Sodium-glucose cotransporter 2 inhibitor (SGLT2) therapy has demonstrated efficacy and safety in the treatment of type 2 diabetes (T2D). Recent studies suggested the potential roles of SGLT2i in the restoration of pancreatic β-cell function. SGLT2i is a new class of antidiabetic agent, independent from insulin action, however, its mechanism is not enough elucidated. We investigated the effects of SGLT2i on pancreatic β-cell function in T2D patients. This open-label, single-arm trial was conducted in our single medical hospital. A total of 30 patients (mean age 57.9±9.0 years, hemoglobin A1c 8.3±1.09%, BMI 29.2±4.5 kg/m², diabetes duration 9.6±7.0 years) received some kinds of SGLT2i, canagliflozin, dapagliflozin or empagliflozin. Any change in the medication of oral hypoglycemic agents was not prohibited during the period of this trial. After 3 months of treatment, changes in hemoglobin A1c, body weight, fat mass, proinsulin-to-C-peptide ratio (ProINS/CPR, as an indicator of distressed pancreatic β-cell) and secretory units of islets in transplantation index (SUIT, as a marker of pancreatic β-cell function) were evaluated. Mean hemoglobin A1c decreased from 8.35 to 7.39% (p<0.01), and body weight decreased from 81.3 to 79.3 kg (p<0.01), significantly. ProINS/CPR ratio decreased from 0.037 to 0.031 (p=0.022), whereas SUIT index restored from 35.3 to 47.8 (p<0.01). We found a linear negative relationship between ΔProINS/CPR ratio and ΔSUIT index (r=-0.338; p=0.01). Multivariate analysis revealed that only baseline ProINS/CPR ratio was independently associated with SUIT index restoration (β=0.673; p<0.01), whereas older age, longer diabetes duration, body weight, fat mass, hemoglobin A1c were not associated. These results suggest that SGLT2i improves pancreatic β-cell function by the relief of β-cell distress, independent of the efficacy of glycemic control and body weight loss effect.

1830-P

Insulin Resistance Impairs Cognitive Performance Even in Healthy Subjects at Risk for Diabetes Mellitus
GIAN PIERO SORICE, ILARIA IMPROTA, TERESA MEZZA, SARA GRIONI, GIOVANNA MURABAYASHI, SATORU MASUSHI, SHO OSONDI, KAZUHIKO TAKAHASHI, HIDEYUKI OTAKA, MIYUKI YANAGIMACHI, HIROSHI MURAOKI, MAKOTO DAIMON, Hiroaki Japan

For this reason 134 (111 F) volunteers, healthy at risk for diabetes mellitus (overweight and/or fasting hyperglycemia and/or family history for T2D, 39.0±12.3 year old, BMI 25.2±4.8 kg/m², were enrolled; they underwent to metabolic study (OGTT for glyceremia, insulinemia and c-peptide), and neuro-psychological tests to evaluate global cognitive function, verbal learning, memory, visual attention and executive functions.

The results of the neuropsychological tests were subsequently normalized by age and education; each test was standardized with a score from 0 (worst) to 4 (best performance). The equivalent scores of each test were summed to obtain a composite endpoint (Cognitive Performance Index, CPI), from 0 to 16, with increasing gradient for better CP. By dividing the subjects recruited into quartiles on the basis of CPI, the IR indexes gradually worsened as CPI became worse, particularly HOMA-IR, Matsuda, basal insulin secretion and basal insulin clearance (<0.04, <0.005, <0.05 and <0.001, respectively). After multiple regression analysis, basal insulin secretion was more related to CP worsening. No correlation with fasting blood glucose, 1 hour and 2 hours glucose after oral load, was found.

These data seem to reinforce the hypothesis that insulin resistance, independently of glyceremia, can worsen performance even in Health subjects, at risk for diabetes mellitus.

1831-P

The Postprandial C-peptide-to-Glucose Ratio Correlated with Beta-Cell Function in Japanese Patients with Type 2 Diabetes Mellitus
YUKI MATSUSHASHI, SHINJI CHIKAZAWA, HIROFUMI NAKAYAMA, MASAYA MURABAYASHI, SATORU MASUSHI, SHO OSONDI, KAZUHIKO TAKAHASHI, HIDEYUKI OTAKA, MIYUKI YANAGIMACHI, HIROSHI MURAOKI, MAKOTO DAIMON, Hiroaki Japan

Though it's possible that the site of degradation (i.e., liver vs. periphery) may change with dose. These data demonstrate that changing concentrations of plasma insulin within physiologic concentrations does not change the rate of insulin removal from the plasma.

1832-P

Heparan Sulfate of β Cells Regulates Insulin Secretion and Contribuates to Normal Glucose Homeostasis
TAKURO MATSUEWA, TAKÉO YOSHIKAWA, AKIRA SUGAWARA, KAZUHIKO VANAI, Sendai, Japan

Heparan sulfate (HS) is a linear polysaccharide and abundantly distributes around cell surface. HS can interact with various bioactive molecules and enhance their signal transduction. Thus, HS is involved in diverse biological functions including development, maturation and proliferation of various tissues. Previous reports demonstrated the expression of HS in β-cells and suggested the possible involvement of HS in functions of β-cells. However, the importance of HS for β-cells remains largely unknown. In the present study, we generated mice with β-cell specific deletion of Ext1 (KO), which encodes an essential enzyme for HS synthesis, to investigate the detailed roles of HS in β-cell development and function. KO mice had decreased body weight despite increased food intake compared to control mice. KO mice showed impaired glucose tolerance associated with decreased insulin secretion upon glucose challenge, without insulin resistance. Glucose-
induced insulin secretion from isolated islets of cKO mice was also significantly reduced. These results indicate the contribution of HS in β-cells to insulin secretion and glucose homeostasis. The expression of several genes essential for glucose-induced insulin secretion was decreased in cKO islets. Pdx1 and MatA, which are important transcriptional factors for β-cell development and maturation, were reduced in cKO islets, indicating HS promotes development and maturation of β-cells. Immunohistochemical analysis of the cKO pancreas revealed reduced β-cell mass and islet number. The percentage of β- and α-positively stained β-cells was decreased in cKO islets, suggesting the involvement of HS in the proliferation of β-cells. Insufficient vascularization in cKO islets might contribute to the abnormal islet architecture. These data demonstrate that HS plays diverse roles in β-cell development and maturation, and that loss of HS leads to insufficient insulin secretion and dysregulation of glucose homeostasis.

**INTEGRATED PHYSIOLOGY—LIVER**

**Moderated Poster Discussion: Integrated Physiology of the Liver**

(Posts: 1833-P to 1838-P, see page 22)

**IGFBP2 Is Increased after Gastric Bypass in Humans—Potential Impact on Hepatic Metabolism**

YOUNG JU, AEKANG CAI, TOKYO TAKAGI, HU PAN, JONATHAN DREYFUSS, KATHLEEN FOSTER, ASHLEY H. VERNON, DONALD C. SIMONSON, ALLISON GOLDFINE, ANDREAS HOEFLICH, MARY E. PATTI, Boston, MA, Cambridge, MA, Dunnemarstorf, Germany

To identify molecular mechanisms contributing to postoperative metabolic improvements after Roux-en-Y gastric bypass (RYGB), we performed comprehensive proteomic analysis of fasting human plasma samples obtained from the SLUMM-T2D longitudinal clinical trial, which randomized obese individuals with T2D to RYGB surgery or a one-year intensive medical diabetes and weight management (DWM) program, and followed them for 3 years. Somatropic proteomic analysis was performed on plasma collected in the fasting state at baseline and during longitudinal follow-up, and proteins differentially abundant in RYGB vs. DWM at each time point were identified. The protein with highest magnitude of differential abundance at 3 years was insulin-like growth factor binding protein 2 (IGFBP2), upregulated by 2.2-fold in RYGB vs. DWM (p=4.37E-96), differences were confirmed by ELISA. IGFBP2 inversely correlated at 3 years with BMI (r=-0.74, p=5.31E-05) and HbA1c (r=-0.68, p=0.00004). Notably, IGFBP2 levels were increased at the first postoperative study visit (10% weight loss) following RYGB or at similar weight loss for the DWM group, suggesting an early weight-independent contribution.

IGFBP2 is predominately expressed in liver and upregulated after RYGB in mice (2.8-fold at 8 weeks, GSE68812). To identify IGFBP2-dependent mechanisms contributing to improved hepatic metabolism, we overexpressed mouse liver fatty acid coactivator (Lepar) or central vector in mouse AkitaMin12 hepatocytes, achieving a 6-fold increase in IGFBP2 protein. qPCR revealed 15-30% downregulation of lipogenic genes (e.g., Fasn, Srebp1) with a 2-fold increase in expression of genes regulating fatty acid oxidation (e.g., Ppara, Ppargc1a). Analysis of metabolism (Seahorse flux analyzer) revealed increased fatty acid oxidation (3-fold, p=0.01 for IGFBP2 vs. control).

In conclusion, increased IGFBP2 expression may contribute to improved hepatic lipid oxidative metabolism, and thus induce systemic metabolic improvement after RYGB surgery.

Supported By: National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases; MedImmune; Sara Elizabeth O’Brien Trust Fellowship

**Hepatic Lipid Profiling in Fatty Liver Disease—Degree of Saturation Matters**

MELISSA L. ERICKSON, JACOB M. HAUS, CHRIS FLASK, JOHN P. KIRWAN, Cleveland, OH, Aukland, MI

Introduction: Hepatic lipids can take on several storage forms, which vary by degree of saturation. The health consequences of hepatic lipids may vary by storage type, in that polyunsaturated lipids may be favorable, while saturated lipids may be detrimental. The purpose of this study was to determine if the degree of hepatic lipid saturation is related to hallmark characteristics of obesity-related nonalcoholic fatty liver disease, including low exercise capacity and insulin resistance.

Methods: Hepatic lipid profiles were measured using 1H-MRS in 30 adults (55 ± 13.4 years, 31 ± 5.5 kg/m²). Methylene, allylic, methylene, and dialytic peaks were quantified. Hepatic lipids were categorized by storage form, including polyunsaturation, unsaturation, and saturation indices. Explored health correlates include exercise capacity, 40 mU/mL euglycemic-hyperinsulinemic clamp, and abdominal CT scans.

Results: 20 participants met the diagnostic criteria for nonalcoholic fatty liver disease (total hepatic fat > 5%). Hepatic polyunsaturation index was positively related to absolute maximal oxygen uptake (r=0.41, P=0.04). In addition, hepatic saturation index was inversely related to clamp-derived skeletal muscle insulin sensitivity (r=-0.40, P=0.07).

Discussion/Conclusion: We found that the hepatic polyunsaturation index was positively related to exercise capacity, independent of body weight. Conversely, saturation index was inversely related to insulin sensitivity. These data show that the health consequences of hepatic fat vary by storage type. Insulin resistance is associated with a higher degree of saturation and a consequential lower degree of polyunsaturation. This suggests effective treatment strategies for nonalcoholic fatty liver disease should not only aim to reduce total hepatic lipid content, but also promote a shift in storage type, from saturation to polyunsaturation, in order to maximize metabolic benefit.

Supported By: National Institutes of Health (R01AD-12804 to J.P.K.); National Center for Research Resources (L58A-1-U1-RR-024890); Case Western Reserve University

**The SGLT2 Inhibitor Canagliflozin Induces Catabolic Transcriptional and Metabolic Switching and Increases FGF-21 in Mice with Dietary Obesity**

SORAVIS OSATAPAN, CHIARA MACCHI, VICENCIA SALES, CHISAYO KOZUKA, JEREMY I. CHIMENE-WEISS, YANNI TANGJAROENPAISAN, JORDAN MORNINSTAR, ROBERT GERSZEN, MARY E. PATTI, Boston, MA, Milan, Italy, Cambridge, MA, Nottingham United Kingdom, Somerville, MA, Brookline, MA

Given the impact of SGLT2 inhibitors to reduce overall mortality and CV risk in T2D, improved understanding of cellular and transcriptional mechanisms responsible for metabolic effects is required. We fed C57BL/6J mice a 60% high fat diet (HFD) for 4 weeks prior to assignment to one of 3 groups: (1) 60% HFD, (2) HFD with canagliflozin (CANA, 25 mg/kg/day), and (3) HFD weight-matched (WM) to CANA via caloric restriction. Mice were analyzed after 4-8 weeks. CANA reduced fasting glucose by 47% (P<0.0001), improved glucose tolerance, and 25% lower body weight vs. HFD (p<0.0001). CANA promoted shift toward lipid utilization, with respiratory quotient -0.7

**Diabetes Remission Clinical Trial (DiRECT)—Plasma Liver Function Tests Reflect Change in Liver Fat Content in Early Type 2 Diabetes**

SVAITALA V, ZHYJINERSKAYA, AHMAD AL-MRABEH, CARL PETERS, ALISON C. BARNES, KIEREN G. HOLLINGTON, HELEN PILKINGTON, PAUL WELSH, NAVEED SATTAR, MICHAEL E. LEAN, ROY TAYLOR, Newcastle upon Tyne, United Kingdom, Glasgow, United Kingdom

We have evaluated changes in liver function tests and liver fat following 12-month weight change in the Tyneside participants of the prospective, randomised Diabetes Remission Clinical Trial (DiRECT). Complete data were available on 45 of the Intervention group participants. The group was typical of early type 2 diabetes: 53.7±1.2 years; 58% male; weight 99.6±2.6 kg; BMI 34.6±0.7 kg/m²; diabetes duration 3.3±0.2 years. Fasting liver fat content was measured by 3-point Dixon MRI.

Baseline fasting plasma glucose was 157±7 mg/dl, with liver fat grossly elevated at 16.2±1.5% (mean±SEM; upper level of normal 5.5%). Mean weight loss was 11.5±1.1 kg (37±2%) and liver fat was normalised at 4.7±0.8% (p<0.001). With weight losses of -30%, -10%, <5%, RYGB, liver fat decreased to 1.9±0.3%, 5.9±1.4% and 10.2±2.2% respectively. ALT decreased by 51% (32.5±3.0 to 16.0±1.1 U/l; p<0.0001), 37% (31.8±3 to 19.3±3.7 U/l; p=0.002), and 35% (24.8±4.7 to 16±1.6 U/l; p=0.058) respectively. Similar reductions were observed in GGT, by 53% (p=0.0001), 35% (p=0.063), 26% (p=0.05) respectively. Lesser changes were observed in AST, by 25% (p=0.001), 25% (p=0.29), and 28% (p=0.012) respectively. There were positive correlations between changes in liver fat and ALT (r=0.5, p<0.0001), GGT (r=0.4, p=0.009) and AST (r=0.4, p=0.016). Change in liver fat correlated with weight change (r=0.5, p=0.0001).

Following weight loss in type 2 diabetes, changes in ALT and GGT reflect change in liver fat even within the normal range. Early type 2 diabetes is associated with severe nonalcoholic fatty liver disease, and monitoring change by a simple inexpensive blood test is important in clinical practice.

Supported By: Diabetes UK

**ADA-Supported Research**

Moderated Poster Discussion
Increased Glucose Homeostasis Is Not an Early Feature of Whole-Body Insulin Resistance in Black Women—The Federal Women Study

STEFANIE T. CHUNG, MCGREY W. HAYMOND, ANTHONY ONZURUIKE, LILLIAN MARBUNDO, H. MARTIN GARRAFFO, PETER J. WALTER, AMBER B. COURVILLE, AHMED M. GABR, SHALI CHACKO, ANNE E. SUMMER, Bethesda, MD; Eden, UT; Houston, TX.

In contrast to white women, fasting hyperglycemia is not an early diabetes risk marker in black women. The etiology of this racial difference in risk is unknown but could be related to differences in rates of gluconeogenesis and hepatic fat in black women. Using stable isotope tracers ([1,4,5,6,7-13C5]glucose, and [13C4]glycerol), we partitioned basal glucose production into its two components (gluconeogenesis and glycogenolysis) and measured basal whole body lipolysis. Whole body (S), hepatic (HIS) and adipose tissue insulin sensitivity were calculated in two groups of federally employed pre-menopausal black women, without diabetes: 24 black and 19 white, age 37±6 (means±SD), range 25-50y; BMI 33±6, range 24.9-45.2 kg/m2. Hepatic and visceral fat were measured by proton MRS. The prevalence of prediabetes (17% vs. 26%, P<0.01), age and BMI were similar in blacks and whites, all P>0.4. Black women had less fasting hyperglycemia (4% vs. 22%, P<0.01), lower visceral and hepatic fat (P<0.01) but similar S, adipose tissue insulin sensitivity and whole body lipolysis (all P>0.5). Basal glucose, insulin and FFA concentrations were similar in both groups (P>0.05). Blacks had lower glucose production (2.52±0.34 vs. 2.75±0.28 mg/kg/min, P<0.05), fractional gluconeogenesis (3.51±0.06 vs. 6.65±1.14%, P<0.02) and absolute gluconeogenesis (1.44±0.28 vs. 1.77±0.31 mg/kgh lean min⁻¹, P<0.01). HIS correlated with S, and hepatic fat (both P<0.05, P=0.01) and the relationship did not differ by race (P<0.05). However, at the same S, blacks had higher HIS (intercepts P=0.01).

In summary, black women had relatively preserved HIS and lower hepatic fat, while white women had higher gluconeogenesis and hepatic fat associated with fasting hyperglycemia. Fasting glucose may be a poor early diabetes marker in black women because gluconeogenesis was low despite whole-body insulin resistance.

Supported By: National Institutes of Health

1837-P

Palmitic Acid Esters of Hydroxy Saturated Acids Are Hepatic Insulin Sensitizers in Chow and High-Fat Diet (HFD)-Fed Mice

ANNA SANTORO, FENG ZHOU, ODILE D. PIRON, ISMAIL SYED, ANDREW T. NELSON, DIONIDIO SIEGEL, ALAN SAGHATELIAN, BARBARA KAHN, BOSTON, MA; La Jolla, CA.

Palmitic acid esters of hydroxy saturated acids (PAHSAs), bioactive lipids with potent anti-inflammatory and antidiabetic effects, reduce ambient glycaemia and improve glucose tolerance and insulin sensitivity in insulin resistant HFD-fed mice. We aimed to determine the mechanisms by which PAHSAs improve insulin sensitivity. We treated chow- and HFD-fed mice with 5-PAHSA (0.1 mg/day) and 9-PAHSA (0.4 mg/day) by SQ osmotic minipumps for 13 weeks. Serum 5-PAHSA levels increased 3.5 fold and 9-PAHSA 2.5 fold in chow-fed mice, while 5-PAHSA levels increased 6 fold and 9-PAHSA 4 fold in HFD-fed mice. PAHSAs had no effect on weight gain or fat mass. We performed hyperinsulinemic euglycemic clamps (2.5 mU/kg/min insulin infusion rate). PAHSA treatment increased systemic insulin sensitivity in both chow- (glucose infusion rate [GIR]: vehicle 13±2 vs. PAHSA 27±4 mg/kg/min) and HFD-fed mice (GIR: vehicle 2±0.5 vs. PAHSA 10±3 mg/kg/min). Endogenous glucose production (EGP) was suppressed 28% in insulin in vehicle-treated mice and 55% in PAHSA-treated mice on chow diet. Remarkably, while insulin failed to suppress EGP in vehicle-treated HFD-fed mice, PAHSA treatment led to a 37% reduction in EGP. PAHSAs also decreased glycemia during a pyruvate tolerance test, indicating that suppression of hepatic glycogenesis contributes to the EGP improvement. Mechanistic studies showed that PAHSAs inhibit basal and glucagon-stimulated EGP and reduce cAMP in isolated hepatocytes. This effect is blocked by pertussis toxin indicating it is mediated by Gαi protein-coupled receptors. PAHSAs also reduce Glpase activity and phosphorylation of CREB in liver. Sum: PAHSAs are systemic insulin sensitizers and augment insulin action on EGP in vivo. In vitro, PAHSAs reduce EGP through a Gαi-dependent pathway involving Gαi protein-coupled receptors. Thus, PAHSAs could be effective antidiabetic agents and the pathways they engage could provide novel drug targets for type 2 diabetes.

Supported By: American Diabetes Association (1-18-RDF-134 to P2) National Institutes of Health (R01DK106210); JPB Foundation; American Heart Association (17POST32850063)

1839-P

A Porcine Placental Extract Alleviates Lipotoxicity-Induced NASH by Polarizing M2 Macrophages and Attenuating Stellate Cell Activation in Mice

GUANLUN CHEN, LIANG XU, NAOTO NAGATA, MAYUMI NAGASHIMADA, TSUJUHITO OTI, KANAZAWA, Japan; ASAHIKAWA, Japan.

NADF is caused by excessive lipolysis and accumulation and associated with activation of macrophage/Kupffer cells and oxidative stress, resulting in nonalcoholic steatohepatitis (NASH) with advanced fibrosis. Placental extracts have been used to treat various chronic diseases due to their antioxidative effect. However, the effects of the extracts on the development of NASH have yet to be elucidated. Here, we investigated the effect of porcine placental extract (PPE) in a lipotoxicity-induced NASH model. C57BL/6 mice were fed a high cholesterol, high-fat (CL) diet or a CL diet containing 0.1% PPE (CL+0.1%PPE) or 0.3% PPE (CL+0.3%PPE). Liver histology and fibrogenesis were examined. In addition, intrahepatic immune cell numbers were quantified by flow cytometry. After 15 weeks of administration, PPE alleviated lipid accumulation by reducing hepatic TG, TC and NEFA levels, as well as lipid peroxidation, which was assessed by TBARS. PPE improved glucose intolerance and enhanced the insulin signal, assessed by IRβ and Akt phosphorylation, in the liver, which was associated with the attenuation of MAPK (ERK/p38MAPK) and NF-κB activation. Flow cytometry analysis revealed that PPE reduced CD11c^+CD206^+M2 (M1) by 44.2%, whereas it increased CD11c^+CD206^−M1 (M2) by 1.4-fold, resulting in a predominance of M2 over M1 macrophage populations in the liver of NASH mice. In addition, PPE downregulated LPS-induced M1 marker mRNA expression in isolated murine peritoneal macrophages, but augmented IL-4-induced M2 marker mRNA expression in a dose-dependent manner. Furthermore, the PPE reduced the hepatic stellate cell (HSC) activation associated with the attenuated transforming growth factor-β1/Smad3 signaling, both in the liver of NASH mice and in HSC line. Thus, PPE may be a potential approach to prevent NASH by limiting lipid peroxidation, promoting M2 macrophage polarization, and attenuating HSC activation.

1840-P

Hepatic G6S2 Exacerbates Hepatic Insulin Resistance in Estrogen-Deficient Female Wistar Rats

HIROAKI SATOH, YOSHIHUKI SUGAYA, CHIHIRO T. MIRIYA, TAKESHI MIYATA, HIROTAKA WATADA, Tokyo, Japan; Fukushina, Japan.

While it has been reported that G0/G1 switch gene 2 (G0S2) inhibited the lipolytic activity of adipose triglyceride lipase, previously, we demonstrated that hepatic G0S2 promotes hepatic insulin resistance by the exacerbation of hepatic steatosis in the high fat diet (HF) fed male Wistar rats. However, the physiological role of hepatic G0S2 is still unknown. Hepatic suppression of G0S2 and novo lipogenesis in the liver and a decrease in serum estrogen levels in menopause is closely associated with the insulin resistance. These findings indicated that postmenopausal hepatic steatosis and insulin resistance are strongly associated with reductions in estrogen levels. To investigate the involvement of hepatic G0S2 in postmenopausal insulin resistance, we studied the effect of G0S2 on insulin sensitivity in HF fed ovariectomized female Wistar rats by overexpressing G0S2 protein using an adenovirus (Ad). Six weeks female Wistar rats were ovariectomized (OVX) or sham operated (O), and maintained on 60% HF for a total of 8 weeks. Ad-G0S2 or control Ad-GFP were injected to these rats after 7 weeks diet challenge. On day 7 post Ad injection, euglycemic-hyperinsulinemic clamp studi...
Reduces Hepatic Collagen in a Mouse Model of NASH

GHARIB, ALICE H. LICHTENSTEIN, ALAN REMALEY, ANNE E. SUMNER, IAN MABUNDO, MAUREEN L. SAMPSON, AMBER B. COURVILLE, AHMED M. ANTHONY ONUZURUIKE, NIRUPA R. MATTHAN, RONALD OUWERKERK, LIL-STEPHANIE T. CHUNG, MIRELLA GALVAN-DE LA CRUZ, SHANNA BERNSTEIN,

In conclusion, hepatic G0S2 exacerbates hepatic insulin resistance only in the estrogen deficient status. The expression level of hepatic G0S2 could affect the development of hepatic insulin resistance in the postmenopausal stage.

Supported By: Japan Ministry of Education, Culture, Sports, Science and Technology (18K08980)

1842-P
MEDI0382, a GLP-1/Glucagon Receptor Dual Agonist, Dramatically Reduces Hepatic Collagen in a Mouse Model of NASH

MICHELLE BEATON, SILVIA GUIDONAU, JAMES P. CONWAY, JOE GRIMSBY, CHRISTOPHER J. RHODES, LUTZ JERMUTUS, JAMES TREVASKIS, GAITHERSBURG, MD; CAMBRIDGE, United Kingdom

Nonalcoholic steatohepatitis (NASH), characterized by hepatic steato- sis, inflammation and fibrosis is an unmet medical need. MEDI0382, a balanced GLP-1/glucagon dual receptor agonist, is under development for the treatment of T2DM. Here we examined the effects of MEDI0382 on NASH compared to iragludine, a GLP-1 analog. Lepin-deficient ob/ob mice were maintained on high trans-fat, fructose and cholester diet for 8 weeks to induce NASH then randomized to four treatment groups: vehicle, MEDI0382 (30 nmol/kg), iragludine (30 nmol/kg) or vehicle-treated and switched to low-fat diet (LFD). Treatment with MEDI0382 and iragludine reduced body weight and improved glucose tolerance. Hepatic lipid was reduced by 40% with MEDI0382 treatment (p<0.0001), which was more effective than ira- gludine or switch to LFD. Hepatic collagen, quantified by type 1 collagen immunohistochemistry, was increased more than 2-fold with NASH and was reduced by 40% in MEDI0382 treated mice (p<0.05). Consistently, type 1 collagen gene expression increased 2-fold with NASH and was reduced by 85% in MEDI0382-treated livers (p<0.001). No reductions in collagen were observed with iragludine or switch to LFD. The NASH score, integrating pathology scores for steatosis, lobular inflammation, fibrosis, hepatocyte ballooning, biliary hyperplasia, and CD68 expression was significantly reduced by MEDI0382 (p<0.001), greater than iragludine or switch to LFD. Consistent with histopathology improvements, MEDI0382 treatment also exerted similar metabolic control relative to ira- gludine, but exhibited superior effects on primary NASH endpoints.

In conclusion, MEDI0382 exerted similar metabolic control relative to ira- gludine, but exhibited superior effects on primary NASH endpoints.

Supported By: National Institutes of Health

1843-P
mGPDH Depress Hepatic Lipogenesis by Inhibition of ER Stress

YI ZHENG, HUINING ZHENG, CHANGPING, China

Background: NAFLD is the most common liver disorder worldwide. Mitochondrial glycerol 3-phosphate dehydrogenase (mGPDH) is a component of respiratory chain, and reported to involve in hepatic glucose homeostasis, however its function in hepatic lipid metabolism is unclear. We previously observed a low mGPDH expression in fatty liver. Thus, this study is to determine the role of mGPDH in liver lipid metabolism and steatosis.

Methods: mGPDH−/− mice were fed chow or HFD. ob/ob and HFD mice were treated adenovirus-associated virus (AAV) 8-mGPDH. Hepatic and plasma lipid profile were assessed. Livers were analyzed by histology, qRT-PCR and immunoblot. RNA-sequencing was performed using hepaticocyte L02 infected mGPDH under FFA.

Results: In fatty livers of NAFLD patients and mice (ob/ob, HFD and db/ db), mGPDH expression is inhibited. Livers of mGPDH−/− mice become sensi- tivity to FFA and adipocyte to steatosis. Mechanistically, RNA-sequencing reveals mGPDH regulates endoplasmic reticulum (ER)-related proteins, and we further confirm its effect on depressing hepatic lipogenesis is mainly through inhibiting ER stress by activation of the IRE1α branch of the UPR. Moreover, rescuing hepatic mGPDH deficient in ob/ob and HFD mice by liver target AAV8 may be a mechanism for ameliorating hepatic steatosis.

Conclusions: mGPDH serves as a novel suppressor for hepatic lipogenesis, and direct targeting of mGPDH may have therapeutic potential for NAFLD.

Supported By: National Key Technology R&D Program of China (2017YFC1009602, 2016YFC1001000), National Natural Science Foundation of China (81470309, 81270893, 81470401, 81700714, 81870873), National Science Foundation Project of Chongqing (CSTC2014JCJJA0006, CSTC2015JCJJA0510, CSTC2016JCYJA0241, CSTC2017JCYJA0192).
Ethnic Differences in Hepatic Insulin Clearance Seen since Child­hood Suggest a Genetic Basis
FRANCESCA PICCININI, DAVID POLIDORI, BARBARA GOWER, JOSE R. FERNAN­DEZ, RICHARD N. BERGMAN, Los Angeles, CA; San Diego, CA; Birmingham, AL

African American (AA) adult women (AAw) have 1/3 the hepatic insulin extraction as European American adult women (EAw). Lower hepatic (but not extrahepatic) insulin clearance in AAw contributes to hyperinsulinemia. Our aim was to examine whether hepatic insulin clearance impairment exists in AA since childhood. If so, genetic factors might explain ethnic dif­ferences in insulin clearance. The FSIGT was performed on 203 children (55 AAe, 88 EAc, 60 HAc (Hispanic American), ages 7-13 years, mean BMI = 19 kg/m², basal plasma glucose = 99 mg/dL, insulin = 78 µU/mL, C-peptide = 511 pM). Data were analyzed with a recent mathematical model providing individual estimates of both hepatic fractional insulin extraction (FE) and hepatic extrahepatic insulin clearance (CE). Results are presented as mean (SD). Two-way ANOVA and ANCOVA were done: sex and ethnicity were used as groups for both the analysis, while age, Tanner stage and body fat from DEXA were the covariates. FE, 
v 0.0007). Adjusting for the covariates, ethnicity was still associated with lower FE in AAc vs. EAc (p = 0.012); sex had a slight but significant effect (FE = 24% (10%) in boys vs. 29% (10%) in girls, p = 0.04). FE, in HAc (28% (21%)) was significantly different than either AAc or EAc (p < 0.05), with or without covariates correction. No correlation between FE, and age was found in these children. Unlike FE, CE, was not impacted by ethnicity or sex; similar values were observed among the three groups (27 (12), 21 (12), and 24 (28) mMol/min for AAc, HAc, and EAc, respectively; p > 0.05). As the between-group differences in FE, are seen early in childhood, this suggests genetic factors likely contribute to those, rather than lifestyle, that might have a more important effect at that age, instead. Playing a more important role than previously realized, the reduced insulin degradation would lead to hyperinsulinemia, insulin resistance, and possibly greater risk for type 2 diabetes in AA, compared to other ethnic groups.

Supported By: National Institutes of Health (R01DK067426, P01DK56336, M01RR00022); National Institute of Diabetes and Digestive and Kidney Diseases (DK72619, DK29667)

INTEGRATED PHYSIOLOGY—LIVER

1845-P The Molecular Role of WNT5A and Its Antagonist SFRPS in Gluco­neogenesis and Inflammation in Human Hepatocytes
MAREN CARSTENSEN-KIRBERG, CORINNA NIERSMANN, KARIN ROEBRING, MICHAEL RODEN, CHRISTIAN HERDER, Düsseldorf, Germany

The wingless-related MMTV integration site (WNT)5A has pro-inflamma­tory effects and induces insulin resistance in mice. The secreted frizzled­related protein 5 (SFRPS) blocks the deleterious effects of WNT5A in mice. In humans, the interaction of WNT5A and SFRPS in the pathogenesis of type 2 diabetes is almost unknown. Therefore, the aim of this study was to characterize the interplay of WNT5A and SFRPS in glucose metabolism and inflammation in human hepatocytes. We treated the human HepG2 cell line without or with (i) 5 nmol/mL WNT5A, (ii) 5000 nmol/mL SFRPS as well as (iii) 5 ng/ mL WNT5A and 5000 nmol/mL SFRPS for 24 h. The mRNA levels of key enzymes of the gluconeogenesis were measured using real-time PCR. We analyzed 92 inflammatory proteins in the supernatant using the OLINK inflammation panel. Total and phosphorylated protein content of markers of inflammatory pathways were analysed using Western blotting. WNT5A increased mRNA levels of phosphoenolpyruvate carboxykinase (PCK2) and glucose-6-phos­phatase catalytic subunit (G6PC) by 50% and 196% compared to control (p<0.05). Interestingly, the co- treatment with SFRPS decreased PCK2 and G6PC mRNA by 36% and 48% compared to control (p<0.05). In addition, WNT5A induced the secretion of protein levels of 23 pro-inflammatory pro­teins in the supernatant on average by 56% compared to control (p<0.05). Most of these proteins were chemokines (e.g., CXCL5, CCL2) and cytokines (e.g., IL-6, IL-18). WNT5A also decreased the phosphorylation level of NF-kB by 39% (p<0.01). The co-treatment with SFRPS led to a secretion profile similar to control. In conclusion, contrary to mouse models, WNT5A has anti-inflammatory properties in human HepG2 which might be mediated by inactivation of the NF-kB signaling pathway. Nevertheless, WNT5A adversely affects the expression of gluconeogenic enzymes. SFRPS antagonizes both beneficial and harmful hepatic effects of WNT5A.

Supported By: German Ministry of Culture and Science of the State of North Rhine-Westphalia; German Federal Ministry of Health; German Federal Ministry of Education and Research

1846-P Exenatide Treatment Improves Mitochondrial Metabolism and Hepatic Insulin Sensitivity in Mice with Nonalcoholic Steatohepa­titis (NASH)
SRILAXMI KALAVALAPALLI, FERNANDO BRIL, ARIANA VERGARA, NISHANTH SUNNY, KENNETH CUSI, Gainesville, FL; College Park, MD

Exenatide (Exe) is a glucagon-like peptide-1 agonist (GLP-1) that enhances insulin production, slows gastric emptying and reduces appetite. Nonalco­holic fatty liver disease (NAFLD), and its more severe form known as NASH, are frequent complications of T2DM. As mitochondrial dysfunction and lipotoxicity are central features of NASH, we tested whether Exe improved mitochondrial oxidative function and hepatic insulin resistance in this set­ting. Mice (C57/B6) were fed either a high-fructose, high trans-fat (TFD) diet for 24 weeks to induce NASH or a control diet. After 16 weeks, mice were randomly assigned for the final 8 weeks to subcutaneous Exe (30 µg/kg/ day) or vehicle. After an overnight fast, mice received an i.v. infusion of [13C3]-propionate and [3,4-13C2]-glucose to evaluate mitochondrial metabolism by NMR-based 13C-isotopomer analysis. Targeted metabolic analysis of lipids was measured by LC-MS/MS. Exenatide reduced liver weight and intrahe­patic triglyceride content (TID: 28%±23 vs. Exe: 19±27 mg/g liver, p=0.03). Fasting plasma glucose, insulin, FFA and TGs were all significantly lower with Exe. Expression of lipogenic genes and inflammatory markers were significantly lowered by Exe. Moreover, Exe reduced hepatic glucose pro­duction, TCA cycle flux, anaplerosis and pyruvate cycling. Exenatide admin­istration improved the lipomic profile, and decreased hepatic byproducts resulting from incomplete fat oxidation (typically associated with insulin resistance/lipotoxicity), such as diacylglycerols (TID: 111±13 vs. Exe: 64±13 µmol/g protein, p=0.02) and ceramides (TID: 1.6±0.1 vs. Exe: 1.3±0.1 µmol/g protein, p=0.02).

Conclusion: In an animal model of NASH, Exe improves hepatic insulin sensitivity, mitochondrial TCA cycle flux and reduces toxic lipid metabo­lates resulting in an improvement of mitochondrial function. Taken together, these results suggest that Exe may be of clinical value in the management of NASH.
Mechanisms of Hepatic Steatosis and Insulin Resistance Induced by Sleep Deprivation in Mice
FUMIKI SHIGIYAMA, NADKI KUMASHIRO, FUKUMI YOSHIKAWA, YOUSUKE TSUNEOKA, HIRONAMI FUNATO, TAKAHISA HIROSE, Tokyo, Japan

Sleep is an important life style component and its deprivation is a risk for type 2 diabetes. However, the underlying mechanisms and the therapeutic target of sleep deprivation induced glucose intolerance are unclear. The aim of this study was to investigate the mechanisms of sleep deprivation induced glucose intolerance focusing on liver. We established a mouse model of sleep deprivation induced glucose intolerance using C57BL/6J male mice. Single 6 hours sleep deprivation by gentle handling method in fasted condition induced glucose intolerance. Interestingly, hepatic glucose production assessed by pyruvate challenge test was significantly increased, and hepatic triglyceride content was also increased in 67% in the sleep deprivation mice compared to freely sleeping control mice. To explore the molecular mechanisms of sleep deprivation induced hepatic steatosis, hepatic metabolites and gene expressions were comprehensively evaluated using metabolome and microarray analyses. Hepatic metabolites such as acetyl CoA, 3β-hydroxybutyric acid, and some acylcarnitines were significantly increased in sleep deprivation group, suggesting increased lipid oxidation in the liver. In contrast, hepatic gene expressions of Elovl3, Lpin1, Plin4, Plin5 and Acot1 that play a lipogenic role were significantly increased in sleep deprivation group, suggesting increased lipid oxidation in the liver. Furthermore, the CANA continuous administration significantly decreased hepatic steatosis and hepatic insulin resistance.

Canagliflozin, an SGLT2 Inhibitor, Prevents Development of Hepatocellular Carcinoma (HCC) from Nonalcoholic Steatohepatitis (NAS) Under Diabetic State
TERUO JUJIMA, SYO WAKAMATU, TOSHIKE IJIMA, ISAO USUI, YOSHIMASA ASO, Mitsubishimoto, Japan

Nonalcoholic steatohepatitis (NAS) can result in liver cirrhosis and hepatocellular carcinoma (HCC). Several studies have shown that some SGLT2 inhibitors alleviate hepatic steatosis or steatohepatitis in type 2 diabetic mice or rats. First, we investigated the effects of canagliflozin (CANA), an SGLT2 inhibitor, on steatohepatitis and fibrosis in a novel diabetes nonalcoholic steatohepatitis (NAS)-HCC progression model mice. Next we investigated inhibitory effects of CANA on development of HCC in this model mice. Mice aged 5 weeks were divided into three groups (vehicle and CANA 30 mg/kg and fed for 3 more weeks). The histological nonalcoholic fatty liver disease activity score (NAS) was lower in the CANA group than in the vehicle group. The expression of type 1 and 3 collagen mRNA was reduced in the CANA group. Mice aged 5 weeks were divided into three groups of 9 animals: vehicle, CANA initial administration 30mg/kg (5 to 9 W), and CANA continuous administration 30 mg/kg (5 to 16 W). At the age of 16 weeks, the NAS was significantly lower in the CANA continuous administration group than in the vehicle group. The CANA administration significantly decreased expression of mRNAs for α-fetoprotein, a tumor maker of HCC, compared with the vehicle administration. In conclusion, canagliflozin attenuates development of NAS showing anti-steatotic and anti-inflammatory effects, and prevents progression of HCC from NAS.

Liver-Specific Overexpression of NOS1AP Alleviates Hepatic Insulin Resistance in Obese Mice
CHEN WANG, Kaida Mu, TianXue ZHOU, Hui ZHU, Weiping JIA, Shanghai, China

Objective: Nitric oxide synthase 1 adaptor protein (NOS1AP) controls a number of different signaling complexes. We reported previously that the NOS1AP SNP rs17243933 was associated with type 2 diabetes (T2D). T2D and nonalcoholic fatty liver disease (NAFLD) are closely associated, in which NAFLD contributes to the development of liver insulin resistance in T2D. Thus, we investigated whether NOS1AP plays a role in regulating hepatic insulin sensitivity.

Methods: Liver-specific NOS1AP overexpression and knockout mice were fed a high-fat diet (HFD).

Results: NOS1AP expression is downregulated in livers of obese rodents. Overexpression of NOS1AP in liver of ob/ob or HFD-induced obese mice improved pyruvate and/or glucose and insulin tolerance, and attenuated liver lipid accumulation in these mice. Conversely, liver specific deletion of NOS1AP impaired pyruvate, glucose and insulin tolerance in the mice, and increased lipid accumulation in the liver. Moreover, overexpression of NOS1AP resulted in reduced expression of Pck1 and increased insulin-induced P-Act in HepG2 cells. Furthermore, the insulin sensitizing effect of NOS1AP could be mimicked by overexpression of C-terminal domain of NOS1AP in ob/ob mice.

Conclusion: Our data demonstrate a novel role of NOS1AP in regulating hepatic insulin sensitivity and lipid accumulation in liver, which implicates NOS1AP a therapeutic target for treatment of NAFLD and prevention of T2D.

Supported By: National Natural Science Foundation of China (81670707)

Hypothalamic Orexin Is Essential for Estrogenic Action on Glucose and Energy Metabolism in Diet-Induced Obese Mice
KANTA KON, HIROSHI TSUNEKI, SHINJIRO TAKATA, TAKAHIRO MAEDA, TSUTOMI WADA, TOSHIYASU SASAKO, Toyama, Japan

Decreased estrogen is a crucial atherogenic factor for type 2 diabetes in postmenopausal women; however, the precise mechanism remains unknown. Orexin is a major hypothalamic neuropeptides regulating energy/glucose metabolism, and its anti-obese effect is more evident in females. We therefore investigated whether estrogen prevents obesity and glucose intolerance through interaction with the orexin system. Ovariectomized (OVX) mice and female orenix knockout (OXKO) mice were prepared to examine the impact of estrogen and orexin deficiency, respectively. When maintained on 60% high fat diet (HFD) for 16-24 weeks, body weight gain, adipose tissue inflammation, and hepatic triglyceride contents were markedly increased in OXKO, compared to wild type (WT) mice. Ovariectomy did not significantly affect the body weight in WT and OXKO mice after prolonged HFD feeding. Importantly, the levels of proinflammatory markers (e.g., TNFα mRNA) in the white adipose tissues were increased mildly in sham-operated OXKO (Sham-OXKO) mice and remarkably in OXV-OXKO mice. The rank order of the severity was OVX-DXKO-Sham-DXKO-DXV-WT-Sham-WT. Moreover, Sirius-Red staining to evaluate the fatty liver disease (i.e., NAFLD/NASH) demonstrated mild and severe fibrosis in the liver of Sham-DXKO and OXV-DXKO mice, respectively, whereas there was no abnormality in OVX-WT and Sham-WT mice. In glucose tolerance test, 1) metabolic activity was greater in Sham-WT than OVX-WT mice, whereas no difference was observed between Sham-DXKO and OXV-DXKO mice on HFD, 2) intracerebroventricular injection of estrogen improved glucose tolerance in OVX-WT but not OVX-OXKO mice on HFD, suggesting that estrogen prevents glucose intolerance on HFD in an estrogen-dependent manner. Taken together, orexin may play a fundamental role in the anti-obese and antiadipogenic effects of estrogen. Therefore, orexin appears to be a novel therapeutic target to prevent metabolic disorders in postmenopausal women.

Lactobacillus Pentosus Strain S-PT84 Attenuates Insulin Resistance and Steatohepatitis by Maintaining Gut Permeability and Polarizing M2 Macrophages
YURIKO SAKAI, MAYUMI NAGASHIMADA, TSUGUHITO OTA, Kanzawa, Japan

Obesity or high-fat diet enhances gut permeability and metabolic endotoxemia, which can trigger insulin resistance and NASH. However, there are few promising treatments targeting lipotoxicity-mediated endotoxemia in NASH. The Lactobacillus pentosus strain S-PT84 has immunomodulatory functions including Th1/Th2 balance modulatory effects and natural killer (NK)/NKT cell activation. In this study, we examined the effect of S-PT84 on diet-induced NASH. C57BL/6 mice were fed a high-cholesterol/high-fat diet (CL) alone or with 1×10^10 S-PT84 (CL + S-PT) for 22 weeks. We quantified intrahepatic immune cells using a fluorescence-activated cell sorter (FACS). S-PT84 administration improved hepatic steatosis by decreasing TGF and FFA levels by 34% and 37%, respectively. S-PT84 also inhibited the development of hepatic inflammation and fibrosis, lowering F4/80 macrophage/Kupffer cell infiltration and the hydroxyproline content of the liver. S-PT84 administration in mice fed a CL diet led to improved hyperinsulinemia as well as...
Elevated Serum Cytokeratin-18 Levels in Patients with Type 2 Diabetes Mellitus and Nonalcoholic Fatty Liver Disease

TAO-CHUN LEE, Pingtung, Taiwan

Background: Cytokeratin-18 (CK-18) is a caspase-cleaved fragment released by injured hepatocytes, and serum levels of CK-18 were believed to be a marker of hepatic cell damage such as inflammation. Patients with type 2 diabetes (T2DM) are well known to have a high prevalence of the fatty liver condition. However, rare studies have been reported the serum CK-18 level in patients with T2DM and investigated the association between the levels with metabolic biomarkers.

Material and Methods: Healthy participants and T2DM patients who followed in the specialized diabetes polyclinic were enrolled. Physical and metabolic factors were collected, and NAFLD was screened by abdominal ultrasound and fatty liver index. Cytokeratin 18 level was detected by commercially available immunoassay.

Results: There were 22.8% (29/127) and 35.9%(42/117) participants were diagnosed with NAFLD in the non-DM group and T2DM group, respectively. Both serum levels of CK-18 M30 and CK-18 M65 were significantly higher in patients with T2DM as compared with those of the non-DM group. Patients with nonalcoholic fatty liver disease (NAFLD) had higher serum CK-18 M30 level whatever withT2DM (205.8±135.1 vs. 108.4±66.19 U/L; P<0.001) or without (177.6±70.53 vs. 87.0±34.57 U/L; P<0.001). Similarly, serum CK-18 M65 was also higher in patients with NAFLD in theT2DM group (513.9±271.2 vs. 285.4±115.3 U/L; P<0.001) and in the non-DM group (353.5±162.4 vs. 248.5±111.3 U/L; P<0.001). Multi-variate regression analyses demonstrated that fasting plasma glucose was independently and significantly associated with CK-18 M30 (β coefficient: 0.002; P<0.001) and CK-18 M65 (β coefficient:0.003; P<0.001). These results suggested that CK-18 level was closely connected with diabetes mellitus.

Conclusions: Independent of NAFLD, our result suggests that CK-18 level was closely associated with the hyperglycemic milieu. The association between serum CK-18 and T2DM may worth for further investigation.
Integrative Physiology—Liver

1857-P
Development of In Vitro NASH Model with Mechanically Compliant Substrate
Masaki Morishima, Kazuki Horikawa, Makoto Funaki, Tokushima, Japan
Although human livers are known to play a role in nonalcoholic steatohepatitis (NASH), understanding of the molecular mechanism of NASH development is incomplete and effective treatment is still greatly sought. Part of this challenging situation in tackling NASH is a lack of an appropriate in vitro hepatocyte culture that reproduces in vivo cellular functions ex vivo. Emerging evidence suggests that matching the stiffness of substrates with that of tissues helps reproducing in vivo functions of cells derived from them. Thus, we hypothesized that primary hepatocytes on 500 Pa polyacrylamide (PAA) gels, whose stiffness matches that of the liver, may exhibit steatosis and a pro-inflammatory response when treated with either fructose or palmitate to model over-nutrition. To this end, rat primary hepatocytes were seeded on either 500 Pa PAA gels or glass coverslips, which represent a conventional but unphysiological stiff culture device. Cells were cultured in low glucose Dulbecco’s Modified Eagle’s medium, whose glucose concentration matches the normal blood glucose level, with or without addition of 5.5 mM fructose or 0.5 mM palmitate. Addition of fructose or palmitate induced lipid accumulation in cells on 500 Pa gels and increased ROS (reactive oxygen species) accumulation in hepatocytes on 500 Pa PAA gels, but not in hepatocytes on glass. Fructose or palmitate treatment also caused HMGB1 (High Mobility Group Box 1) secretion by hepatocytes, implicating a pro-inflammatory response by these cells. These results suggest that exposure of hepatocytes on a mechanically compliant substrate to either fructose or palmitate may serve as an excellent ex vivo model of the initial phase of NASH development by showing ability to initiate an inflammatory process.

1858-P
PBI-4547 Improves Glucose Metabolism and Insulin Resistance, and Reduces Liver Damage in a High-Fat Diet Mice Model of Obesity and Metabolic Syndrome
Martin Leduc, Brigitte Groulx, Mikael Tremblay, Juliette Gervais, François Sarrà-Bournet, Alexandra Felton, Jean-Christophe Simard, François A. Léblond, Pierre Larin, Lynne Gagnon, Oscar De, Canada
Introduction and Aims: Obesity and its resulting metabolic disturbances are major health threats and are the main cause of a host of diseases, including nonalcoholic fatty liver disease (NAFLD). PBI-4547 is a novel first-in-class orally active antidiabetic compound which displays pleiotropic activities and has been shown to reduce NASH, diabetes, and renal fibrosis in different animal models. The aim of this study was to investigate the effects of PBI-4547 in a mouse model of high-fat diet-induced obesity and metabolic syndrome.

Methods: C57BL/6 mice were fed with either a standard or a high-fat diet (HFD), Harlan, TD.06414) for 14 weeks. These mice were divided in three groups [normal chow, HFD + vehicle, and HFD + PBI-4547 (10 mg/kg, oral once a day)] and treated for an additional 6 weeks. Blood glucose, serum insulin level, serum triglyceride and adiponectin, liver histology, as well as liver and white adipose tissue (WAT) pro-inflammatory/ fibrotic gene expression were examined.

Results: In oral glucose tolerance test, PBI-4547 increased glucose metabolism compared to the HFD control group. Insulin resistance [measured by HOMA-IR] and β cell function [HOMA1-β] were improved by PBI-4547. Serum total cholesterol level was significantly reduced by PBI-4547 while adiponectin in serum was significantly increased. Histological analysis showed a significant reduction of hepatic steatosis and ballooning by PBI-4547. To further characterize the activity of PBI-4547, quantitative RT-PCR analysis of pro-fibrotic markers was performed, demonstrating that PBI-4547 reduced CTGF and MMP2 gene expression in the liver as well as CTGF, MCP-1, MMP2, and collagen type I gene expression in the WAT.

Conclusions: Taken together, these results suggest that PBI-4547 offers the potential as a novel therapy for nonalcoholic fatty liver disease, obesity and associated metabolic syndrome.

1859-P
A Novel Role for SerpinB1, a Protease Inhibitor, in Hepatic Biology
Kazuki Drime, Dario F. de Jesus, Rohit Kulkarni, Boston, MA
SerpinB1, a protease inhibitor that is secreted from the liver in response to insulin resistance, was recently reported to promote pancreatic β cell proliferation. We focused on investigating the significance of SerpinB1 in the liver to gain insights into its role in regulating whole body metabolism. We determined SerpinB1 gene expression in multiple metabolic tissues harvested under fasting or fed states from ~34-week-old male Liver-specific insulin receptor knockout (LIRKO) mice and littermate controls. While in controls SerpinB1 expression was reduced by ~50% after feeding when compared to the fasting state, (P<0.02, n=4-5), the LIRKOs, in contrast, exhibited a 2.3-fold higher (P<0.01, n=5-6) expression in the fed vs. fasting states and the higher levels were consistent with earlier observations in the LIRKO livers. We next took advantage of the availability of liver samples from 18 to 24-week-old male SerpinB1 KO mice and littermate controls and subjected them to RNA sequencing. As expected, SerpinB1 gene expression was absent in the KO samples, and interestingly, was associated with a significant decrease in gene expression related to cell cycle, NF-κappa B signaling, and inflammatory pathways. Independent validation of these data by RT-PCR confirmed a decrease in cell cycle-related genes such as Ccn2 (1.46, P<0.04), Ccnb2 (-54%, P<0.04), Ccn1 (-46%, P<0.03), and Ccne1 (-51%, P<0.07), and the cell proliferation marker, MkI67 (67%, P<0.01) (n=5). Furthermore, knockdown of SerpinB1 in the human hepatocyte cell line, HepG2, exhibited significantly decreased expression of Ccnb2 (-38%, P<0.01), Ccnb2 (-44%, P<0.01), Ccne1 (-21%, P<0.00), MkI67 (-30%, P<0.00), and MCM2 (-29%, P=0.00) genes, and increased expression of P21 (+165%, P<0.00) (n=3 for control vs. knockdown groups). These novel data implicate endogenous SerpinB1 in cell proliferation in hepatocytes and warrant further investigation of its role in hepatocyte proliferation and the overall impact on glucose homeostasis.

1860-P
Growth Differentiation Factor 15 Ameliorates Nonalcoholic Steatohepatitis Associated with Metabolic Syndrome in Mice
Myung-Shik Lee, Yong-Ho Lee, Seong Hun Kim, Kook Hwan Kim, Seoul, Republic of Korea
Growth differentiation factor 15 (GDF15) is an endocrine hormone belonging to TGFβ superfamily member. GDF15 administration or GDF15 overexpression has been reported to have anti-obesity and antidiabetic effects. Although nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH) is frequently associated with metabolic syndrome or diabetes, the functional role of endogenous GDF15 and therapeutic effect of exogenous GDF15 in NASH associated metabolic syndrome have not been addressed. We studied whether GDF15 has therapeutic effects on NASH and associated metabolic syndrome.

To this end, Gdf15-knockout and Gdf15-transgenic mice were employed, and mice were fed Amin liver NASH (AMLN) diet as a physiologically relevant dietary mouse model of NASH associated with metabolic syndrome. GDF15 expression was increased in the livers of mice fed AMLN diet and human subjects with NASH. Elevated expression of GDF15 was due to diet-induced endoplasmic reticulum (ER) stress in the liver. Importantly, Gdf15-knockout mice exhibited deteriorated metabolic syndrome and aggravated NASH phenotypes such as increased steatosis, hepatic inflammation, fibrosis and liver injury. Furthermore, we found that GDF15 directly suppresses expression of fibrosis-related genes and osteopontin (OPN) in the liver in vivo. OPN expression was increased in hepatocytes and stellate cells in the liver of Gdf15-knockout mice. Finally, we found that GDF15-transgenic mice showed attenuated NASH phenotypes and improved glucose tolerance in mice fed AMLN diet. Our results suggest that induction of endogenous GDF15 is a compensatory mechanism to protect against NASH associated with metabolic syndrome and that GDF15 could be an attractive therapeutic candidate for treatment of these diseases.

Supported By: Korean National Research Foundation

1861-P
Liver-Specific siRNA Inhibition of Class 2a Histone Deacetylases (HDACs) Reduces Expression of Genes Regulating Gluconeogenesis in Primary Human and Mouse Hepatocytes, but Not in Mice
Sven W. Görgens, Surajprakash RaiChaur, Paulus Wohlfart, Bodu Brunner, Norbert Tenagailles, Maximilian Bieholfi, Frankfurt, Germany
Gene expression control by histone-deacetylases Class 2a (HDACs 4,5,7,9) has been demonstrated to be involved in the negative regulation of hepatic gluconeogenesis and consequently inhibition of HDACs was shown to result...
in improved glucose and pyruvate tolerance in rodent type 2 diabetes (T2D) models. However, pan-inhibition of HDACs in all tissues leads also to severe side effects in various tissues, excluding this approach for treatment of T2D. Here, we have investigated in vitro and in vivo safety and efficacy of a liver-selective HDAC knock-down via single or combinatorial siRNAs for HDAC 4, 5 or 7. In primary mouse and human hepatocytes, specific siRNAs directed against HDAC 4, 5 or 7, as well as their combination led to a selective knock-down of the respective target gene(s) by about 80-90%, which paralleled with a significant reduction of genes involved in the regulation of gluconeogenesis. These siRNAs were administered in a liver-specific lipid-particle formulation for treatment of healthy C57BL/6J mice. Mice received five intravenous injections with either PBS, a control siRNA, one of the respective silencing siRNAs (0.75mg/kg) or all possible dual or triple combinations for 25 days. Quantitative real-time PCR demonstrated that siRNA treatment led to a significant downregulation of the respective HDACs in the liver. However no reduction of gluconeogenic genes (PCK1 and G6PC) was detected. Consequently, also no improvement in intraperitoneal pyruvate tolerance test (PTT) could be observed. In addition, no significant differences in fasting blood glucose or plasma insulin were observed between treatment groups.

In summary, although active in cellular systems, liver-targeted siRNA knockdown of class 2a HDACs did not result in a clear inhibition of genes regulating gluconeogenesis in healthy mice suggesting no clear path forward for development of this approach for treatment of T2D.

1862-P Difference in Hepatic Steatosis and Pancreatic Beta-Cell Mass between Dapagliflozin and Insulin Glargine Treatment at Comparable Levels of Glycemic Control
KAZUO OKU, AKINUSHI NAKAMURA, HIDENORI MIYOSHI, KIYOHIKO TAKASHI, NAOYUKI KITAO, YASUO TERAUCHI, TATSUYA ATSUMI, Sapporo, Japan, Yokohama, Japan

Background: Although several studies have shown that SGLT2 inhibitors exert protective effects on pancreatic beta cells and hepatic steatosis, the mechanism remains unknown. Therefore, we compared the glucose-lowering effect of the SGLT2 inhibitor dapagliflozin (dapa) on pancreatic beta cell mass and hepatic steatosis with those of insulin glargine.

Methods: Six-week-old db/db mice were assigned to one of four groups: untreated (Placebo), treated with dapa (Dapa), treated with insulin glargine (Gla), or treated with both dapa and insulin glargine (Dapa+Gla). After 8 weeks of treatment, we determined blood glucose levels, beta cell mass, and liver triglyceride content.

Results: Fed blood glucose levels were significantly lower in the treated groups compared with the Placebo group (Placebo 304.2 ± 35.6 mg/dL, Dapa 425.0 ± 28.7 mg/dL, Gla 406.1 ± 25.8 mg/dL, Dapa+Gla 347.3 ± 24.0 mg/dL). Immunohistochemical analysis revealed that pancreatic beta cell mass was significantly increased in the Dapa and Dapa+Gla groups, but not in the Gla group, compared with the Placebo group (Placebo 2.25 ± 0.45 mg, Dapa 5.01 ± 0.92 mg, Gla 3.79 ± 0.32 mg, Dapa+Gla 5.19 ± 0.56 mg). Liver TG content was significantly increased in the Gla group compared with the placebo group (Placebo 24.1 ± 5.7 mg, Dapa 30.6 ± 6.4 mg, Gla 128 ± 25 mg, and Dapa+Gla 54.4 ± 7.1 mg per gram liver). Microarray analysis revealed genes involved in hepatic steatosis such as Cidec and Pparg were significantly upregulated in the Gla group compared with the Placebo group. As for hepatic fatty acid composition, concentrations of C16:0 and C18:1n-9 were significantly increased in the Gla group compared with the Placebo group, while C18:0 was not significantly different between groups. There was no difference in safety including mortality.

Conclusion: Beta cell mass was maintained, and hepatic steatosis was not induced, after 8 weeks of treatment with dapa, but with insulin glargine, in db/db mice.

Supported By: AstaZeneca

1863-P Regulation of Hepatic Insulin Sensitivity and Hepatic Steatosis byULK1
YOUNGDO KOO, MICHAEL P. GARNEAU, QUANJIANG ZHANG, E. DALE ABEL, Iowa City, IA

Hepatic insulin resistance (IR) plays a central role in the pathophysiology of impaired glucose tolerance, type 2 diabetes and nonalcoholic fatty liver disease (NAFLD) and steatohepatitis (NASH), which is emerging as a major cause of liver failure and hepatocellular carcinoma. Impaired autophagy may also contribute to hepatic insulin resistance, but the interactions between insulin sensitivity and autophagy are incompletely understood. The Unc-51 Like Autophagy Activating Kinase 1 (ULK1) is an early stage autophagosome formation related kinase that is activated in selective autophagy and may be independent of nutrient or energy status. We observed that in addition to its role in autophagy regulation, ULK1 may also directly regulate insulin signaling by modulating Akt dephosphorylation. Specifically, silencing ULK1 significantly impaired insulin-stimulated activation of Akt and GSK3β in hepatocytes in the absence of significant changes in autophagy. To understand the role of ULK1 in hepatic insulin action ULK1 liver specific knock-out mice were generated. Body weight increased in L-ULK1KO relative to wild type mice on normal chow diet or 60% high fat diet. L-ULK1 KO mice exhibited impaired glucose tolerance and insulin resistance. Serum concentrations of insulin, triglyceride, cholesterol, AST and ALT were increased. Phosphorylation levels of FoxO1 and FoxO3a were decreased in concert with increased expression levels of PEPCK and G6Pase and increased hepatic glucose production. In contrast, L-ULK2 KO mice were phenotypically normal. Thus, ULK1 independently and directly regulates hepatic insulin sensitivity and glucose homeostasis.

1864-P Genetic Ablation of Liver CPT-1A Gene Protects Mice against High-Fat Diet-Induced Obesity and Insulin Resistance
DONGHA WU, Guangzhou, China

Carnitine palmitoyl transferase 1A (CPT-1A) catalyzes the transfer of the acyl group of long-chain fatty acid-CoA moiety onto carnitine, an essential step for the uptake of long-chain fatty acids and their subsequent beta-oxidation in the mitochondrion. It is the rate-limiting step in beta-oxidation and is highly expressed in the liver where it plays an important role in triglyceride metabolism. The physiological consequences of CPT-1A deficiency in liver, however, are yet to be reported. In this study, we have generated mouse model with liver specific deletion of CPT-1A gene. We found that deletion of CPT-1A in liver caused an increased triglyceride content in liver and decreased epididymal adipose tissue weight compared with control mice under high fat diet feeding conditions. RNA-seq analysis between livers of CPT-1A knockout vs. wild type mice revealed altered expression of many metabolic pathways such as steroid hormone biosynthesis and PPARG signaling pathways as well as some novel hepatokines. Further analysis of the significance of these changes is under way but the data so far suggest that a pharmacological agent that alters hepatic fatty acid oxidation (perhaps acting on CPT-1A) could provide a novel approach to target nonalcohol fatty liver disease (NAFLD).

1865-P WITHDRAWN
Liver fibrosis is the result of chronic liver injury and the first step toward the development of liver cirrhosis and hepatic carcinoma. Under the stress of damage factors, quiescent hepatic stellate cells (qHSCs) trans-differentiate into myofibroblast-like cells, and take the main role of extracellular matrix secretion contributing to the development of liver fibrosis. In recent clinical study, circulating level of A-FABP, was found to positively correlate with the stages of liver fibrosis and liver cirrhosis. Here, we investigated the role of A-FABP in the development of liver fibrosis. A-FABP knockout (A-FABP KO) mice and their wild type (WT) littermates were subjected to bile duct ligation (BDL) for two weeks to induce liver fibrosis. Plasma and hepatic A-FABP were significantly elevated in BDL treated WT mice. Liver sinusoidal endothelial cell (LSEC) was identified as the major cellular source of hepatic A-FABP in response to BDL. In the BDL treated groups, comparing to the WT mice, A-FABP KO mice showed significantly reduced collagen formation and HSC activation which were accompanied by an attenuated induction of hepatic expression of transforming growth factor beta 1 (TGFβ1), a central regulator in hepatic fibrogenesis. As the LSECs and HSCs are closely attached to each other, we hypothesize that LSECs-derived A-FABP may act in a paracrine manner to stimulate the expression of TGFβ1 in HSCs. Our in vitro study demonstrated that treatment of recombinant A-FABP protein (rA-FABP) significantly induced the expression of TGFβ1 in primary HSCs. Mechanistically, BDL induces the release of A-FABP from LSECs which stimulates the TGFβ1 gene transcription through enhancing the activator protein-1 (AP-1) activity on its promoter via upregulating the phosphorylation of c-Jun, a component of AP-1.

In conclusion, A-FABP contributes to the development of liver fibrosis via enhancing the expression of TGFβ1 in HSCs.

Supported By: Health and Medical Research Fund of Hong Kong (G0137086)

1876-P cGMP-Dependent Protein Kinase I (cGKI) Modulates Human Hepatic Stellate Cell Activation
ANDRAS FRANKO, MARKETA KOVAROVA, ROBERT WAGNER, CORA WEIGERT, ROBERT FEI, SUSANNE FEI, HANS-ULRICH HAERING, STEFAN Z. LUTZ, ANDREAS PETER, Tübingen, Germany
Background: Nonalcoholic fatty liver disease and hepatic insulin resistance precede diabetes and may further develop into nonalcoholic steatohepatitis and liver fibrosis/cirrhosis. The activation of hepatic stellate cells (HSC), which is characterized by the loss of retinyl-ester stores, plays a crucial role in the pathophysiology of this process. Since cGMP-dependent protein kinase (cGKI) deficient (cGKI-KO) mice displayed hepatic insulin resistance and disturbed glucose metabolism, as well as cGKI is only detected in HSC but not in hepatocytes, we hypothesized that cGKI modulates HSC activation and its metabolic consequences.

Methods: First, retinyl storage and gene expression were studied in cGKI-KO mice. Second, we investigated the effects of cGKI-silencing on gene expression and cellular activation in the human stellate cell line LX2. Finally, cGKI expression was investigated in human liver biopsies covering a wide range of liver fat content.

Results: Retinyl-ester level in the liver of cGKI-KO mice was lower compared to wild type animals, which was associated with increased inflammatory gene expression. Activation of LX2 cells showed increased a-smooth muscle actin and matrix metalloproteinase 2 expression, which was augmented by silencing cGKI. On the other hand, activation of LX2 cells by TGFβ suppressed cGKI expression. Furthermore, we detected a negative correlation between cGKI mRNA and liver fat content in human biopsies.

Conclusions: The lower mRNA level of cGKI either in TGFβ activated LX2 cells or in liver biopsies with high fat content suggest that cGKI function might be impaired during HSC activation. Furthermore, the higher expression of inflammatory genes and low retinyl-ester levels in cGKI-KO mice as well as the higher levels of activation markers in cGKI-silenced LX2 cells indicate that cGKI inhibits HSC activation. Since cGKI is a downstream target of nitric oxide (NO), it is conceivable that NO may exert protective effects inhibiting liver fibrosis via cGKI.

Supported By: German Center for Diabetes Research

1867-P Lean Subjects with Fatty Liver Show Decreased GLP-1 and GIP Response during OGTT
AMALIA GASTALDELLI, JESUS GARDUNO-GARCIA, RALPH A. DEFRONZO, JENS H. HOLST, NICOLAS MUSI, San Antonio, TX, Copenhagen, Denmark
Subjects with nonalcoholic fatty liver disease (NAFLD) are at high risk of type 2 diabetes even if they are not obese and recent studies have indicated that liver fat (LF)>2.5% was already associated with alteration in glucose and insulin metabolism. Our aim was to investigate if having LF as low as 2.5% was associated to impairment in insulin sensitivity, secretion (ISR) and/or incretin hormones glucagon-like peptide (GLP) 1 and glucose-depended insulino tropic peptide (GIP) released during an oral glucose tolerance test (OGTT).

We studied 49 nonobese subjects (age 52±4; BMI 24.2±0.4 kg/m²). All subjects underwent a 2 h OGTT with plasma insulin, C-peptide, GLP-1, and GIP concentrations were measured every 15-30 min and ISR was quantitated by C-peptide deconvolution. Insulin sensitivity was quantified by HOMA and Matsuda index. Liver fat (LF) accumulation was quantified by magnetic resonance spectroscopy (MRS).

In this group of non-obese subjects the great majority were non-NAFLD (31 had LF<2.5%, while 18 had NAFLD (9 had LF 2.5-5% and 9 had LF>5%). Age, BMI, HOMA (1.4±0.2 vs. 1.1±0.2), Matsuda index (7.3±0.7 vs. 10.6±1.3), fasting glucose (5.2±0.1 vs. 5.2±0.1 mmol/l), insulin (8.1±0.7 vs. 4.7±0.7 mU/l), ALT (20±1 vs. 19±1 U/l) and TG (96±22 vs. 88±8 mg/dl) were similar in NAFLD and non-NAFLD.

Subjects with LF>2.5% had lower GLP-1 [GLP-1_AUC0-120 was 2.8±0.3 vs. 3.7±0.3, p=0.03], insulin secretion [ISR_AUC0-120 was 61±5 vs. 78±5 nmol, p=0.03] and insulin clearance [MCRI0-120 69±6 vs. 91±7 ml/kg/min, p=0.01] but not GIP [GIP_AUC0-120 was 4.6±0.3 vs. 5.3±0.3, p=ns] response compared to NAFLD. glucose and insulin concentrations during OGTT were similar [Glucose0-120 6.7±0.3 vs. 7.3±0.3 mmol/l; Insulin0-120 39.9±3.7 vs. 37.5±3.3 mU/l].

Conclusions: Liver fat accumulation (LF>2.5%) is associated with reduced GLP-1. ISR and MCRI, this can help to explain the increased risk of T2D of subjects with NAFLD.

Supported By: ADA-Supported Research
1870-P
Short-Term Exercise Improves Hepatic Insulin Extraction in Individuals with Nonalcoholic Fatty Liver Disease

ADITHYA HARI, CIARAN E. FEALEY, JOHN P. KIRWAN, Cleveland, OH

Nonalcoholic fatty liver disease (NAFLD), the hepatic component of insulin resistance syndrome, is pathophysiologically associated with lower hepatic insulin extraction, lower fat oxidation and increased carbohydrate oxidation in a post-absorptive state. Aerobic exercise is purported to be beneficial in NAFLD. To better understand the mechanisms through which short-term, moderate intensity aerobic exercise training could exert these benefits, 13 obese, sedentary adults (age: 58±3.4 years, BMI: 34.3±1.1 kg/m2; mean±SEM) with NAFLD (>5% Intra-hepatic lipid content assessed by 1H MR spectroscopy) were recruited into a 7-day exercise training program (treadmill walking for 80 mins, 5 days per week, at 60-85% maximum heart rate). Participants maintained their normal dietary patterns. Pre- and post-intervention assessments included a 75-gm OGTT, CT scans, VO2max, and indirect calorimetry. Insulin sensitivity (ISI) was estimated using Soonthornpun model. Hepatic Insulin Extraction (HE) was calculated as the molar difference in AUCs for insulin and C-peptide (HE=1-(AUCinsulin/AUCC-peptide)).

The intervention yielded an ~9% increase in VO2max and HE (P<0.01). Whole-body insulin sensitivity increased by ~43% (P<0.01). There was a significant increase in basal fat oxidation (pre vs. post: 47±6 vs. 65±6 mg/min, P<0.05) and decrease in basal carbohydrate oxidation (150±20 vs. 112±15 mg/min, P<0.05). After the intervention, HE was positively correlated with adiponectin (r=0.56, P<0.05) and negatively correlated with TNF-α (r=-0.78, P<0.001). The change in ISI was negatively correlated with change in subcutaneous abdominal fat depot (r=-0.55, P<0.05). These data suggest that exercise may quickly reverse the pathophysiology of NAFLD by improving HE and fasting substrate oxidation. The cardio-metabolic benefit of exercise in individuals with NAFLD is potentially mediated through changes in HE.

Supported By: National Institutes of Health (R01DK120834)

1871-P
Liver-Specific Overexpression of 17β-HSD13 Causes Hepatic Steatosis in Mice

WEN SU, YOUNG GUJAN, SHENTHEN, China; DALIAN, China

According to our previous study, considerable evidences showed that a liver lipid droplet-associated protein 17β-HSD3 contribute to the development of liver disease. To understand the basis for this, we generated and studied transgenic mice that express human hsd17b3 specifically in hepatocytes (L-H17B13 mice). We examined the hepatic expression of several genes involved in fatty acid synthesis and oxidation in L-H17B13 mice. mRNA levels of three enzymes involved in fatty acid synthesis (SRBP1c, fatty acid synthase [FAS], and ACC) were significantly increased in L-H17B13 mice. The mRNA levels of peroxisomal proliferator-activated receptor α (PPARα), a transcription factor that promotes fatty acid oxidation and its target gene, acyl-CoA oxidase (ACOX) and medium-chain acyl-CoA dehydrogenase (MCAD), also higher in L-H17B13 mice. mRNA levels of carnitine palmitoyltransferase (CPT1a), a protein involved in translocating fatty acids into the mitochondria for oxidation, was higher in L-H17B13 mice. ApoA1, a lipid secretion related gene, was markedly reduced in L-H17B13 mice. Strikingly, male liver-specific h17β-HSD3 mice fed a standard chow diet display significantly elevated hepatic triglyceride levels at 3-4 months of age compared to matched littermate controls. When mice were fed a high-fat diet, this hepatic phenotype, as well as other metabolic phenotypes (obesity and glucose intolerance), worsened. Our investigations establish that 17β-HSD3 specifically overexpressed in mice hepatocytes induces hepatic steatosis and metabolic disorders.

1872-P
A Role for Macrophage Adenosine 2A Receptor in Diet-Induced Nonalcoholic Fatty Liver Disease

JING ZHU, HONGGUI LI, XIANJUN LUO, LINQIANG MA, CHAOONG WU, College Station, TX

Recent evidence suggests that adenosine 2A receptor (A2AR) exerts a protective role in NAFLD. However, the role of the A2AR in macrophages in NAFLD pathophysiology remains unknown. In the present study, hepatic inflammation and fat deposition were examined in myeloid cell-specific A2AR-deficient mice and control mice fed a HFD for 12 weeks. In addition, bone marrow cells were isolated from global and/or myeloid cell-specific A2AR-deficient mice and differentiated into macrophages (BM-MDA) for inflammatory analysis and for macrophage-hepatocyte co-cultures. Upon HFD feeding, the activity of JNK p65 and NFκB p65 and the mRNA levels of proinflammatory cytokines such as TNFα, IL-1β, and IL-6 in livers of myeloid cell-specific A2AR-deficient mice were significantly higher than their respective levels in livers of control mice. These increases were accompanied with increased severity of diet-induced hepatic steatosis, indicated by the results from liver histology and by elevated levels of liver triglycerides. When BM-MDA were analyzed for inflammatory activation, the phosphorylation states of JNK p65 and NFκB p65 and the production of proinflammatory cytokines in A2AR-deficient BM-MDA were significantly higher than their respective levels in control BM-MDA. Moreover, in macrophage-hepatocyte co-culture systems, hepatocytes co-cultured with A2AR-deficient BM-MDA revealed significant increases in TNFα, IL-1β, and IL-6 mRNAs in relative to hepatocytes co-cultured with control BM-MDA. Additionally, hepatocytes co-cultured with A2AR-deficient BM-MDA accumulated much more fat upon palmitate stimulation than hepatocytes co-cultured with control BM-MDA. Taken together, these results suggest that the inflammatory status of macrophages can be altered by A2AR in a manner to critically determine the development of NAFLD. Moreover, targeting A2AR to suppress inflammation may be a viable preventive and/or therapeutic approach for inflammation-associated diseases including NAFLD.

Supported By: American Diabetes Association (1-17-IBS-145 to C.W.); National Institutes of Health

1873-P
Metabolic Dysfunction within Brown Adipose Tissue and Skeletal Muscle Caused by Complete Hepatic Insulin Resistance Is Reversible by FGF-21 Treatment

OLIVER STUDER, RONGYA TAO, KYLE D. COPPS, MORRIS F. WHITE, Boston, MA

Hepatic insulin resistance is a major factor in the pathogenesis of type 2 diabetes and obesity. However, the role of the liver in the development of insulin resistance in the periphery is not well understood. One factor contributing to elevated BCAA in obesity and diabetes is increased hepatic insulin resistance, which can impair muscle and adipocyte metabolism. To determine the importance of hepatic insulin resistance in these processes, we generated LDKO-mice, a model for hepatic insulin resistance. LDKO-mice display improved glucose tolerance, insulin sensitivity, and glucose uptake into BAT. However, LDKO-mice have reduced fuel oxidation and reduced glucose uptake into skeletal muscle. In addition, LDKO-mice have reduced heat production in BAT and reduced glucose uptake into BAT. These results suggest that reduced glucose uptake into BAT and skeletal muscle is responsible for the reduced fuel oxidation. FGF-21 treatment can restore and improve glucose metabolism despite the persistent hepatic insulin resistance and uncontrolled gluconeogenesis in these mice.

Supported By: National Institutes of Health

1874-P
Integration of BCAA and Lipid Metabolism by the BCKDH Kinase and Phosphatase

PHILLIP J. WHITE, ROBERT W. MCCARRAH III, PAUL A. GRIMSRUD, WEN-HSUAN YANG, GIO-FANG ZHANG, JONATHAN M. HALDEMAN, MICHELLE ARLOTTO, OLGA ILKAYEVA, RICHARD M. WYNN, DAVID T. CHUANG, CHRISTOPHER B. NEWGARD, Durham, NC; Dallas, TX

Strong associations exist between branched chain amino acids (BCAA) and dysregulated glucose and lipid metabolism, but underlying mechanisms are not well understood. One factor contributing to elevated BCAA in obesity is inhibitory phosphorylation of the branched chain ketone-acid dehydrogenase complex (BCKDH) in liver. We studied the impact of modulating the activity of the BCKDH kinase (BOK) and phosphatase (PPM1K) on amino acid, glucose and lipid metabolism in Zucker fatty rats (ZFR). Daily administration of a selective inhibitor of BOK, BT2 (20mg.kg^-1 IP), for one week or expression of a recombinant adenovirus overexpressing PPM1K significantly lowered BCAA and branched chain keto acid (BCKA) levels in the ZFR. Reciprocally, these effects were accompanied by strong lowering of liver triglycerides and improved glucose tolerance in the absence of weight loss. Proteomics analysis of liver samples from these studies revealed that both inhibition of BOK with BT2 and adenoviral mediated overexpression of PPM1K results in...
red phosphorlization of the lipogenic enzyme ATP-citrate lyase (ACL) on its regulatory serine 454. Phosphorylation of ACL on this site is activating. Sequence analysis revealed the presence of a canonical BDK phosphorylation motif surrounding ser454 in ACL and incubation of ACL with purified BDK resulted in ACL phosphorylation in vitro. Furthermore, adenosine-metabolized overexpression of BDK increased ACL phosphorlization and activated de novo lipogenesis in liver of lean Wistar rats. Together these studies reveal a fresh regulatory function for BDK and PPMK in integration of BCAA and lipoid metabolism. Moreover, we show that modulation of this node provides broad protection against metabolic abnormalities associated with obesity.

Supported By: American Diabetes Association/Pathway to Stop Diabetes (1-18-INI-17 to P.J.V); National Institutes of Health (P01DK58398)

1876-P Simultaneous 1H and 13C Metabolic Flux Analysis of Liver Metabolism Using NMR and GC-MS—Methods Validation and New Applications

STANISLAW DEJA, JUSTIN A. FLETCHER, BLANKA KUCEJOVA, XIAORONG FU, College Station, TX; Guangzhou, China; Houston, TX

Hepatic metabolism is critically altered by the pathology of many diseases, including obesity, diabetes and NAFLD. Quantitative estimation of gluconeogenic flux and TCA cycle turnover are clinically useful parameters as they represent major biosynthetic and energetic pathways that are perturbed by these diseases. NMR spectroscopy is an important technique used to study hepatic fluxes since it can precisely distinguish between 1H and 13C metabolic tracers, and provide position-specific enrichment. However, the throughput of NMR for flux analysis is hindered by its low sensitivity, requiring microscale experiments that have limited biological mass (e.g., primary hepatocytes, tissue biopsies or mouse blood analysis) often infeasible. Thus, we investigate an alternative approach based on GC-MS measurements of glucose mass isotopomers and mathematical modeling of metabolic fluxes. In contrast with NMR, MS approaches are very sensitive, but cannot directly distinguish nuclei and provide position-specific enrichment information. Hence, we validated a GC-MS method in isolated perfused mouse liver and in vivo infusions in rats against NMR measurements. A medium-scale metabolic network containing atom transitions for both hydrogen and carbon atoms in the gluconeogenic pathway and TCA cycle was able to deconvolute 1H and 13C labeling information and estimate metabolic fluxes. Although some fluxes were significantly different between the NMR and GC-MS, there was excellent correlation between the two approaches. Finally, we applied GC-MS based simultaneous 1H and 13C approach in primary mouse hepatocytes cultured in 60 mm dishes, an experiment not feasible using standard NMR equipment. This opens future possibilities for drug screening and translational flux studies.

Supported By: National Institutes of Health (R41EB015908, R01DK078148); Robert A. Welch Foundation (j-1804)

1877-P Differential Effects of Niacin on High-Fat Diet-Induced Adipose Tissue Inflammation and Nonalcoholic Fatty Liver Disease in C57BL6/J and B612SFF2/J Mice

HAN FANG, EMILY GRAFF, ZHUOYUE LI, ROBERT L. JUDD, Auburn, AL

Pharmacological doses of niacin improve insulin resistance (IR) and reduce body weight, hyperglycemia, and liver triglyceride content in rodent models of obesity/T2DM. Niacin improves insulin sensitivity by targeting Akt and AMPK pathways. This effect is compromised in T2DM, which may be due to the increased oxidative stress in the liver. We investigated whether differences in glucose metabolism exist between T2DM rats treated with niacin and T2DM rats with normal liver Glc-6-Pase activity.

Supported By: American Diabetes Association/Pathway to Stop Diabetes (1-18-INI-17 to P.J.V); National Institutes of Health (P01DK58398)

1878-P Glutathione Deficiency Induces Epigenetic Alterations of Vitamin D Metabolism Genes in the Liver of High-Fat Diet-Induced Type 2 Diabetic Mice

RAJESH PARSANATHAN, SUSHIL K. JAIN, Shreveport, LA

Vitamin D (VD) deficiency is an epidemic health problem. Over a billion people worldwide are VD-deficient or insufficient. VD regulates the function of over 200 genes and is essential for growth and development. VD-deficiency can result in diabetes, hypertension, heart disease and stroke. VD levels correlate positively with GSH and negatively with insulin resistance in type 2 diabetic mice. HD-fed mice exhibited elevated blood glucose, and decreased blood GSH and 25(OH)VD with reduced GSH and increased oxidative stress in the liver. We investigated whether GSH deficiency induces epigenetic alterations in VD-metabolism genes in the high-fat diet (HFD) fed mice. The levels of VD-metabolism genes (CYP2R1, CYP27A1, CYP27B1, and VDR) and GSH biosynthesis pathway genes (GCLC, GCLM, GSTs, and GSR) were significantly (p<0.005) down-regulated in the liver of HFD-fed mice. Conversely, CYP24A1 which metabolizes the active VD was significantly (p<0.005) increased. In vitro mouse hepatocyte GCLC knockdown decreases GSH and alters VD-regulatory genes in the similar pattern of HFD-fed mice. Further, significant increased CYP24A1 expression in HFD-fed mice with reduced GSH and increased oxidative stress in the liver. We investigated whether GSH deficiency induces epigenetic alterations in VD-metabolism genes in the high-fat diet (HFD) fed mice. The levels of VD-metabolism genes (CYP2R1, CYP27A1, CYP27B1, and VDR) and GSH biosynthesis pathway genes (GCLC, GCLM, GSTs, and GSR) were significantly (p<0.005) decreased in the liver of HFD-fed mice compared with control (normal diet) group. GSH deficiency-induced epigenetic alterations (methylation status) of VD-metabolism enzyme genes and the VDR gene appear to play a significant role in the circulating VD. These findings indicate that GSH epigenetically regulates VD-metabolism genes in obesity/T2DM and a novel therapeutic target for restoring VD-deficiency in susceptible populations.

Supported By: National Institutes of Health; National Center for Complementary and Integrative Health (R01AT004742, 2013-16); Louisiana State University Health Sciences Center, Shreveport

ADA-Supported Research
Moderated Poster Discussion
Impact of Hepatic Mig6 on Glucose Homeostasis and Oxidative Stress
JOSE M. IRIMA-DOMINGUEZ, ANDREW J. LUTKESWITTE, PATRICK T. FUEGER, Duane, CA, St. Louis, MO

Hepatic epidermal growth factor receptor (EGFR) expression and activation are decreased during steatosis in humans and several animal models of obesity. Restoring EGFR activation in obesity-induced endoplasmic reticulum (ER) stress and diabetes is a potential therapy to improve liver function in type 2 diabetes (T2D). Metinogenic-inducible gene 6 (Mig6) is an inducible feedback inhibitor of EGFR activity and, therefore, a target for enhancing EGFR signaling during diet-induced obesity and T2D. We previously observed that liver Mig6 expression was increased during obesity-induced insulin resistance in C57Bl/6J mice fed a high fat diet and by both pharmacological- and fatty acid-driven ER stress in hepatocytes, leading to decreased EGFR-mediated EGFR activation. To test the hypothesis of Mig6 as a target to treat insulin resistance in T2D, we examined liver-specific Mig6 knockout mice (LKO) and their littersmate controls (CON) during diet-induced obesity.

We identified enhanced whole-body glucose tolerance and hepatic insulin action in LKO compared to CON mice. Moreover, liver ballooning, an oxidative stress marker, was also improved in LKO mice. Using whole transcriptome sequencing, we sought to determine the molecular mechanisms leading to liver function improvement in obesity-induced insulin resistance in LKO mice. We identified that gene expression and protein accumulation of key enzymes of both peroxisomal (e.g., Acox1, Ehhadh) and mitochondrial (e.g., Cpt1a, Cacld) beta-oxidation were decreased by Mig6 ablation. This observation correlated with a compromised gene expression of liver gluconeogenic enzymes.

In conclusion, we posit that hepatic Mig6 deficiency partially reverts the effects of obesity-induced diabetes by decreasing hepatic glucose output and reducing cellular oxidative stress, thereby establishing Mig6 as a therapeutic candidate for treating insulin resistance in obesity and T2D.

Supported By: National Institutes of Health (DK99301 to P.T.F.)

A Novel Mechanism by Foxo1 Phosphorylation Mediates Glucagon Signaling in Control of Glucose Homeostasis
YUKIN WU, HUI YAN, QUAN PAN, HONGTING ZHENG, SUDATH A. Dahanayake, CHONGQING, China

Glucagon increases hepatic glucose production (HGP) to maintain blood glucose homeostasis. The forkhead transcription factor Foxo1 promotes HGP through increasing expression of genes encoding the rate-limiting metabolic enzymes for gluconeogenesis. We previously established that insulin suppresses Foxo1 by Akt-mediated phosphorylation at Ser256 in human hepatocytes. Here we demonstrated glucagon promotes Foxo1 nuclear translocation and stability-dependent phosphorylation of Foxo1 at Ser276, serving as a novel mechanism of glucagon action in control of glucose homeostasis. In vitro protein kinase assay showed a direct phosphorylation of Foxo1 at Ser276 by PKA. Replacing Foxo1-Ser276 with alanine (S276A) or asparagine (S276N) reduced or increased Foxo1 stability in human hepatocytes, respectively. To establish the in vivo function of Foxo1-Ser276 phosphorylation in glucagon metabolism, we generated Foxo1-S277A and Foxo1-S273D knock-in mice, revealing the novel mechanism by which glucagon, via PKA-dependent phosphorylation of Foxo1 at Ser276, promotes Foxo1 nuclear localization, stability, and HGP. Thus, Foxo1-Ser276 is a potential target site for the control of Foxo1 bioactivity and associated metabolic diseases.

Supported By: National Institutes of Health

Protection of Induction of Oxidative Stress in Diet-Induced Obese Mice by a Low-Iron Diet
LIPKAA SALAYE, IZELZAVETA BYCHKOVA, FELIPE LORENZO, SANDY T. SINK, DÖN MCLAIN, Winston-Salem, NC, Salt Lake City, UT

Iron is a risk factor for type 2 diabetes, but its relationship to other aspects of metabolic syndrome is less clear. To investigate iron’s relation to nonalcoholic steatohepatitis (NASH), mice were fed a “fast food” (FF)-diet (40% energy as fat, 12% SFA, 0.2% cholesterol, and 18.9 g/L glucose and 23.1 g/L fructose in their drinking water) for 10 or 24 weeks. The diets contained either 4 low iron, UI, 35 (normal iron, NI) or 2000mg iron/kg chow (high iron, HI). HOMA-IR values were 2.2-fold higher (p<0.01) in the FF-groups at 10 weeks, but did not increase further with HI (1.18-fold, p=0.5). At 10 weeks all groups had similar glucose excursions during glucose and pyruvate tolerance testing. There was no significant difference in IP-ITT or IPP-TT area under the glucose curve. Liver triglycerides (TG) were significantly increased by FF (4.2-fold, p<0.01) but not iron at 10 weeks. The effect of FF was greater at 24 weeks (22.4 fold p<0.001), and at 24 weeks iron further increased liver TG [3.3 fold HIIF vs. LIF, p<0.001]. A marker of liver injury (ALT) increased 10.3-fold (p<0.001) on the HIIF diet compared to NI normal chow, but only 3.2- fold (p<0.05) on LIF. The fibrotic gene collagen/alpha was increased 14.3-fold (p<0.01) in HIIF but not at all (0.8-fold) on LIF compared to HI normal chow. Similar protection was afforded by the L diet to increases in expression of the inflammatory genes TGF-beta and TNF-alpha seen in HIIF. RNA sequencing data revealed transcriptional regulation of a large family of fat metabolic genes by FF, whereas only the TGF-beta signaling pathway was significantly altered by iron content. We conclude that dietary iron restriction can protect from NASH induced by a high-fat and -carbohydrate diet. A likely candidate mechanism is through a known mediator of hepatic fibrosis, TGF-beta.

Supported By: National Institutes of Health, U.S. Department of Veterans Affairs

Pyruvate Carboxylase Is Required for Hepatic Gluconeogenesis and TCA Cycle Function
DAVID CAPPEL, STANISLAW DEJA, XIANGONG FU, SHAWN C. BURGESS, Dallas, TX

Production of glucose by the liver is crucial for maintaining whole-body glucose homeostasis and is dependent on carbon substrates provided by anaplerotic pathways into the TCA cycle. In the liver, the large majority of anaplerotic flux is through the conversion of pyruvate to oxaloacetate by the action of pyruvate carboxylase (PC). To investigate the role of PC in hepatic gluconeogenesis, we produced a liver-specific PC knockout mouse (LPCKO). LPCKO mice have impaired ability to convert pyruvate into glucose. Surprisingly, they display no difference in blood glucose under fed and overnight fasted conditions. LPCKO mice, however, have elevated concentrations of ketone bodies in plasma under both fed and fasted conditions, suggesting a switch from gluconeogenesis to ketogenesis. Additionally, we observed changes in kidney gene expression that suggest a compensatory upregulation of renal gluconeogenesis. Using stable isotope tracers, we analyzed anaplerotic and TCA cycle fluxes in LPCKO livers and found that LPCKO livers are deficient in anaplerotic flux and have a large reduction but not total ablation of hepatic gluconeogenesis. The LPCKO livers also show a significant reduction in TCA cycle turnover and reduced concentrations of several TCA cycle metabolites. On a high-fat diet (HFD), LPCKO mice gain slightly less weight than their non-transgenic littermates. After 12 weeks of HFD the LPCKO mice have significantly lower blood glucose and plasma insulin compared to non-transgenic littermates. When subjected to a glucose tolerance test, HFD-fed LPCKO mice show significantly better glucose tolerance than non-transgenic littermates. Overall, we demonstrate that flux through hepatic PC is required for anaplerosis and TCA cycle function in the liver and that restricting hepatic gluconeogenesis and TCA cycle turnover may help to protect against the deleterious metabolic effects of high fat diet.

Supported By: National Institutes of Health (F22DK105741R01, DK078184

Xbox-Ser253 Phosphorylation Regulates Glucose Homeostasis in Mice
HUI YAN, YUKIN WU, QUAN PAN, ZHEM SHEN, HONGTING ZHENG, MORRIS F. WHITE, YUKIANG SUN, SHADONG GUO, SR., College Station, TX, Belfast, United Kingdom, Chongqing, China, Boston, MA

The forkhead transcription factor Foxo1 is a key mediator in insulin signal- ing pathway that controls hepatic glucose production (HGP) and pancreatic beta-cell function. Upon activation of the protein kinase Akt, insulin promotes glycogen synthesis and inhibits gluconeogenesis in the liver, reducing blood glucose. We previously demonstrated human Foxo1-Ser253, an equivalent to mouse Foxo1-Ser253, is a key phosphorylation site for insulin and Akt suppression, promoting Foxo1 nuclear export and suppressing the expression of the target gene for liver gluconeogenesis. Here we investigated the role of Foxo1-Ser253 phosphorylation in control of glucose homeostasis in vivo, by generating Foxo1-S253A and knock-in (KI) mice, in which Foxo1-Ser253 replaced by alanine (A mutation) that blocks phosphorylation. Foxo1-S253A mice displayed mild increases in feeding blood glucose and insulin level, but reductions in fasting blood glucose and glucagon concentration, as well as a decrease in the ratio of the number of pancreatic α-cells/β-cells per islet. Foxo1-S253A mice exhibited slight increases in insulin sensitivity but barely changed glucose uptake among tissues, and an enhanced energy expenditure. Further analyses indicate that Foxo1-S253A-enhanced Foxo1 activity and promoted the effect of glucagon on HGP. This is the first report demonstrating that Foxo1-Ser253 phosphorylation status itself is sufficient to affect HGP and glucose homeostasis, as well as regulate the synthesis of insulin and glucagon in vivo.

Supported By: National Institutes of Health

INTEGRATED PHYSIOLOGY—LIVER
Sex Differences in the Response of C57BL/6 Mice to Ketogenic Diets

JESSE COCHRAN, PAUL V. TAUFELLE, KEVIN D. LIN, YUAN ZHANG, E. DALE ABLE, Iowa City, IA, Nashville, TN

Since the initial use of ketogenic diets (KD) as adjunctive treatment for epilepsy, these diets are being increasingly used to promote weight loss and to reduce the risk of metabolic sequelae of obesity. Typical KD are very low in carbohydrate and high in fat, promoting hepatic production of ketone bodies. Few studies have evaluated gender differences in response to KD, and many animal studies tend to be performed in male mice. To explore sex differences in response to KD, female and male wild type mice on the C57BL/6J background were fed either a control diet (CD: 7% fat, 47% carb., 19% protein) or KD (75% fat, 3% carb., 8% protein), following weaning. Females on the CD manifested higher levels of circulating β-hydroxybutyrate (β-HB) than males (2.86-fold, p<0.05). Circulating β-HB concentrations increased with KD in males and females (1.30-fold and 5.05-fold, p<0.01 and p<0.01 respectively) with higher concentrations in females. After 8 weeks, females on KD displayed an increase in body weight (1.07-fold KD vs. CD, p<0.05) while body weight declined in males (0.88-fold, p<0.05). Nuclear magnetic resonance analysis revealed elevated lean mass in females (1.07-fold, p<0.05), but no significant reduction in fat mass in males (0.49-fold, p<0.05) relative to sex-matched mice on CD. The female mice on KD developed impaired glucose tolerance with a 1.35-fold increase in glucose tolerance test area under the curve (GIT AUC) relative to females on CD (p<0.001). In contrast, fasting glucose levels were lower in males on KD (151.8 ± 12.5 mg/dl vs. 169.2 ± 6.3 mg/dl, p<0.05). Despite no significant change in GIT AUC, the male mice on KD displayed elevated blood glucose concentrations 30 minutes after injection relative to males on CD (344.9 ± 18.7 mg/dl vs. 272.0 ± 10.3 mg/dl, p<0.05). However, after 120 minutes, blood glucose levels returned to initial fasting levels.

In conclusion, significant sex differences exist in terms of body composition and metabolism in response to ketogenic diets via mechanisms that remain to be elucidated.

Supported By: American Heart Association

Protein and Glucose Absorption and Gastrointestinal Hormone Secretion Differ between Roux-en-Y Gastric Bypass and Sleeve Gastrectomy

MARIA S. SUYANE, KIRSTINE N. BOLSEN-MOLLER, CHRISTOFER MARTINUSSEN, CARSTEN DIRKSEN, SØREN REITELSEDER, LARS HOLM, VIGGO B. KRISTIANSEN, GERRIT VAN HALL, JENS J. HOLST, STEN MADSBAD, SR., CARSTEN DIRKSEN, SØREN REITELSEDER, LARS HOLM, VIGGO B. KRISTIANSEN, GERRIT VAN HALL, JENS J. HOLST, STEN MADSBAD, SR., Hvidovre, Denmark, Copenhagen, Denmark, Birmingham, United Kingdom

Sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) induce comparable weight loss and improvements in glycemic control despite marked differences in gastrointestinal rearrangements. We hypothesized that absorption rates of oral glucose and protein derived amino acids (AA) were accelerated after both procedures resulting in comparable gut hormonal responses. 12 SG and 12 RYGB operated and 12 control (C) subjects carefully matched on BMI, age, sex and post-operative weight loss showed primed-continuous infusions of stable isotopes of glucose, phenylalanine (phe), tyrosine and urea combined with a 6-hour mixed meal test (400 kcal, 50%carb, 35%fat, 15% protein) containing a glucose isotope and intrinsically phe labelled casein. Peak rate of appearance (Ra) of oral glucose was higher after RYGB and SG compared with C (RYGB 861 ± 130 µmol/kg FF/Min, SG 271 ± 221; p<0.05 for all comparisons) and peak Rg of phe originating from meal protein was higher after RYGB but similar in SG and C (RYGB 0.33±0.04, SG 0.17±0.02, C 0.13±0.01 p<0.01 for RYGB vs. both SG and C). Oral recovery of ingested glucose and phe as well as protein synthesis were clearly enhanced within the first postprandial hour after RYGB, whereas total net protein balance and oral recovery did not differ between groups. Urea turnover was equal between groups. The rapid absorption of glucose and phe was associated with larger but more transient excursions of plasma glucose and AAs followed by increased lactate formation and higher secretion of GLP-1, insulin and PYY, exclusively after RYGB. Ghrelin concentration was lower after SG. Postprandial glucose and protein metabolism and gastro-entero-pancreatic hormone secretion clearly differ after RYGB and SG, with accelerated absorption of glucose and casein after RYGB, whereas casein uptake after SG resembled controls. Hence different mechanisms may underlie the improved glycemic control and weight loss after RYGB and SG.

Supported By: European Research Council (695069)

Impact of Type 1 Diabetes on 24-Hour Energy Expenditure and Metabolic Flexibility

ELVIS A. CARNERO, KAREN D. CORBIN, CHRISTOPHER P. BOCK, STEVEN R. SMITH, RICHARD E. PRATLEY, Orlando, FL

Type 1 diabetes (T1D) is associated with an increase in resting metabolic rate, but the impact of T1D on other components of 24-hour energy expenditure (EE) and metabolic flexibility (MF) is not known. We measured 24-hour EE, its components and substrate oxidation rates in 11 patients with T1D and 12 nondiabetic, age and BMI matched controls (RO) using whole room calorimetry. MF was defined as the respiratory quotient (RG) kinetic response after ingesting a standard high CHO breakfast. Briefly, the kinetics between the lowest RG pre-breakfast and the highest RG after breakfast were analyzed by a simple linear regression between time (1-minute resolution) and RG units (ROLLins). Subjects with T1D had marginally higher 24-hour EE and higher 24-hour non-exercise EE, but sleeping EE and basal EE were not significantly different (Table 1). There were no differences in 24-hour respiratory quotient (RG) or sleeping RG, but MF during the breakfast meal was significantly lower in T1D vs. HC (p=0.042). Among patients with T1D, MF was related to the glycemic response to breakfast. These data suggest that T1D is characterized by alterations in EE and MF. These results have implications for glycemic and weight management among patients with T1D.
Meal Intake Is Suppressive of Ketogenesis in Patients with Type 1 Diabetes
HUSAMI GHANIM, KELLY GREEN, JEANNIE M. HJENA, NITESH D. KUHADIYA, MANAV BATRA, AJAY CHAUDHURI, PARESH DANDUNA, Buffalo, NY, Williams-ville, NY, New York, NY

Aim: To investigate whether the intake of a meal suppresses ketogenesis in patients with type 1 diabetes.

Methods: 30 patients with type 1 diabetes with no C-peptide, fasted overnight, were divided into 3 groups of 10 patients each. The first (group 1) continued the fast for 5 hours after arrival in our clinical research unit while the second (group 2) was administered a high fat high calorie (HFHC) meal without prandial insulin and the third (group 3) was administered the meal with prandial insulin. Blood samples were obtained prior to and after the meal at hourly intervals for 5 hours.

Results: In group 1, glucose and glucagon concentrations remained unchanged while FFA concentrations increased (by 74±16%) as did acetocetate (AcAc) and beta-hydroxybutyrate (BHB) concentrations (by 52±13% and 64±16%, respectively). In group 2, the intake of the meal without prandial insulin induced marked increase in glucose, glucagon and FFAs (by 232±32%, 81±18% and 75±17%, respectively) concentrations. However, the meal induced significantly lower increase in AcAc or BHB concentrations (increased by 29±3% and 35±11%, respectively) compared to group 1. In group 3, given prandial insulin before the meal, there was a significant reduction in glucose and glucagon concentrations as compared to group 2 and a fall in FFA concentrations (by 41±12%) below baseline levels. There was no significant increase in AcAc and BHB.

Conclusions: While a prolonged fast was associated with maintenance of glucose and increases in FFA, AcAc and BHB concentrations, the intake of the meal prevented increases in AcAc and BHB in spite of increases in glucose, glucagon and FFA concentrations. These actions are consistent with an anti-ketogenic effect of the meal intake even in type 1 diabetes with an absence of β cell function.

Releasing Disinhibited Eating Behaviors to Resting State Functional Connectivity in Young Children
ALLISON L.B. SHAPIRO, SUSAN L. JOHNSON, BRIANNE MOHL, GRETA WILKENING, KRISTINA T. LEGET, DANA DABELEA, JASON R. TREGELLAS, Aurora, CO

The prevalence of obesity among children in the United States is alarming, with recent work implicating disinhibited eating behaviors (DEBs) as a potential pathway toward obesity development. DEBs have been documented among young children, and are associated with longitudinal weight gain. However, the underlying neurobiology of DEBs in young, healthy weight children, prior to obesity development, remains unknown. This study investigated the relationship between DEBs and intrinsic neuronal connectivity in young children. We tested the hypothesis that greater DEBs would be positively associated with higher neuronal connectivity in the default mode network (DMN) and the salience network, and lower connectivity in the executive control network. The Eating in the Absence of Hunger paradigm was implemented to measure DEBs, with post-lunch calories consumed from highly palatable foods used as our main predictor. Resting state functional magnetic resonance imaging was used to examine neuronal connectivity in the DMN, the salience network, and the executive control network. The Eating in the Absence of Hunger paradigm positively associated with higher neuronal connectivity in the default mode network (DMN) and the salience network, and lower connectivity in the executive control network.

Meal Intake Is Suppressive of Ketogenesis in Patients with Type 1 Diabetes
HUSAMI GHANIM, KELLY GREEN, JEANNIE M. HJENA, NITESH D. KUHADIYA, MANAV BATRA, AJAY CHAUDHURI, PARESH DANDUNA, Buffalo, NY, Williams-ville, NY, New York, NY

Aim: To investigate whether the intake of a meal suppresses ketogenesis in patients with type 1 diabetes.

Methods: 30 patients with type 1 diabetes with no C-peptide, fasted overnight, were divided into 3 groups of 10 patients each. The first (group 1) continued the fast for 5 hours after arrival in our clinical research unit while the second (group 2) was administered a high fat high calorie (HFHC) meal without prandial insulin and the third (group 3) was administered the meal with prandial insulin. Blood samples were obtained prior to and after the meal at hourly intervals for 5 hours.

Results: In group 1, glucose and glucagon concentrations remained unchanged while FFA concentrations increased (by 74±16%) as did acetocetate (AcAc) and beta-hydroxybutyrate (BHB) concentrations (by 52±13% and 64±16%, respectively). In group 2, the intake of the meal without prandial insulin induced marked increase in glucose, glucagon and FFAs (by 232±32%, 81±18% and 75±17%, respectively) concentrations. However, the meal induced significantly lower increase in AcAc or BHB concentrations (increased by 29±3% and 35±11%, respectively) compared to group 1. In group 3, given prandial insulin before the meal, there was a significant reduction in glucose and glucagon concentrations as compared to group 2 and a fall in FFA concentrations (by 41±12%) below baseline levels. There was no significant increase in AcAc and BHB.

Conclusions: While a prolonged fast was associated with maintenance of glucose and increases in FFA, AcAc and BHB concentrations, the intake of the meal prevented increases in AcAc and BHB in spite of increases in glucose, glucagon and FFA concentrations. These actions are consistent with an anti-ketogenic effect of the meal intake even in type 1 diabetes with an absence of β cell function.

Relating Disinhibited Eating Behaviors to Resting State Functional Connectivity in Young Children
ALLISON L.B. SHAPIRO, SUSAN L. JOHNSON, BRIANNE MOHL, GRETA WILKENING, KRISTINA T. LEGET, DANA DABELEA, JASON R. TREGELLAS, Aurora, CO

The prevalence of obesity among children in the United States is alarming, with recent work implicating disinhibited eating behaviors (DEBs) as a potential pathway toward obesity development. DEBs have been documented among young children, and are associated with longitudinal weight gain. However, the underlying neurobiology of DEBs in young, healthy weight children, prior to obesity development, remains unknown. This study investigated the relationship between DEBs and intrinsic neuronal connectivity in young children. We tested the hypothesis that greater DEBs would be positively associated with higher neuronal connectivity in the default mode network (DMN) and the salience network, and lower connectivity in the executive control network. The Eating in the Absence of Hunger paradigm was implemented to measure DEBs, with post-lunch calories consumed from highly palatable foods used as our main predictor. Resting state functional magnetic resonance imaging was used to examine neuronal connectivity in the DMN and the salience network, and lower connectivity in the executive control network. The Eating in the Absence of Hunger paradigm positively associated with higher neuronal connectivity in the default mode network (DMN) and the salience network, and lower connectivity in the executive control network.
Dietary fat type (SFA, MUFA, n-3 PUFA, n-6 PUFA, and trans FA) was calculated with food records (5±2 days [mean±SD]) in 106 federally employed women (53% African American, 14% African immigrants, 33% white). Dietary fat type was assessed with food records (5±2 days [mean±SD]) in 2 groups of women of African descent (blacks) compared to whites. Results: Individuals with the most and least improved biomarkers showed no significant difference in model-estimated energy balance or in self-reported lifestyle at baseline. Neither caloric deficit nor linear combinations of model-estimated parameters were predictive of outcomes, showing the value of our complex physiological model for prediction. The model suggests that unique sets of optimal diets exist for achieving individual health goals (Figure 1).

**Figure 1.** Optimized Changes in Fat and Carbohydrate Intake for Two Individuals to Reduce Body Weight by 5-7%.

**Comparison of Dietary Fat Intake Using Food Records vs. RBC Fatty Acid Biomarkers in a Multiethnic Population—The Federal Women Study**

AMBER B. COURVILLE, SHANNA BERNSTEIN, MIRELLA GALVAN-DE LA CRUZ, ANTHONY ONUZURUIKE, NIRUPA R. MATTHAN, ALICE H. LICHTENSTEIN, ANNE E. SUMNER, STEPHANIE T. CHUNG, BETHESDA, MD

Erythrocyte membrane fatty acids (RBC FA) may be a useful biomarker of dietary fat type to assess its impact on health and disease. Our objective was to examine the association of dietary fat type and RBC FA composition in 2 groups of women of African descent (blacks) compared to whites. Dietary fat type was assessed with food records (5x2 days [meansSD]) and RBC FA composition (mol%) by gas chromatography in 106 federally employed women (53% African American, 14% African immigrants, 33% white; age 44±8y, range 24-82y; BMI 30.5±4.9 kg/m², range 20.3-45.2 kg/m²). Dietary fat type (SFA, MUFA, n-3 PUFA, n-6 PUFA, and trans FA) was calculated as a proportion of total dietary fat. Blacks reported consuming higher SFA and n-6 PUFA (all P<0.05). Dietary report of MUFA, trans FA or n-3 PUFA intake were similar by race (all P>0.20). In contrast, when RBC FA composition was measured, blacks had higher MUFA and n-3 PUFA (both P<0.05). RBC composition of SFA, n-6 PUFA and trans FA were similar by race (all P>0.05). Spearman correlations were calculated to determine the relationship between dietary FA and RBC FA. There was a positive correlation between dietary FA and RBC n-6 PUFA (r=0.3, P<0.02).

In summary, RBC FA was a good marker of n-6 PUFA intake, however, food records appeared to provide a more informative assessment of overall dietary fat type exposure.

Supported By: National Institutes of Health

**In summary, RBC FA was a good marker of n-6 PUFA intake, however, food records appeared to provide a more informative assessment of overall dietary fat type exposure.**

**1893-P**

Comparison of Dietary Fat Intake Using Food Records vs. RBC Fatty Acid Biomarkers in a Multiethnic Population—The Federal Women Study

**1894-P**

The Different Effects of Sodium Glucose Cotransporter 2 Inhibitor on Obese Diabetic Mice Fed a Normal or Low-Carbohydrate Diet

FUTOSHI FURUYA, YOSHIMITO FUJITA, NAOMI MATSUO, YASUO OGURI, HIROTO MINAMINO, KAORI IKEDA, SHINICHI HARASHIMA, YU WANG, YANYAN LIU, NOBUYU IAIGAKI, KYOTO, Japan

Sodium glucose co-transporter 2 inhibitors (SGLT2i) are antidiabetic drugs for type 2 diabetes that lower blood glucose levels and induce weight loss. However, the efficacy of SGLT2i is known to be affected by dietary factors such as carbohydrate and fat intake. In this study, we compared the effects of the SGLT2i (dapagliflozin) in eight-week-old male KK-Ay mice (a diabetic obese model) pair-fed a normal carbohydrate diet (NCD; carbohydrate 65, protein 23, fat 12%) or a low carbohydrate diet (LCD; carbohydrate 20, protein 45, fat 35%) for 8 weeks with or without dapagliflozin (5 mg/kg p.o.; n=5-6). Dapagliflozin reduced body weight gain and blood glucose levels in the fed state in NCD and LCD, but reduced fasting blood glucose levels in NCD only. Likewise, dapagliflozin ameliorated glucose intolerance and enhanced hepatic gluconeogenesis in NCD only. Dapagliflozin decreased serum LDL cholesterol levels and subcutaneous fat in both groups, but decreased epididymal fat (a visceral fat) in NCD only. We then investigated the metabolic effects of dapagliflozin and their underlying mechanisms in liver using transcriptomics (DNA microarray analysis) and metabolomics (Capillary Electrophoresis-Mass Spectrometry: CE-MS and Liquid Chromatography-Mass spectrometry: LC/MS). Dapagliflozin upregulated the expression of genes related to gluconeogenesis and β-oxidation in liver in both groups. In NCD, dapagliflozin increased several kinds of amino acids, and in LCD, it increased ketone bodies. Dapagliflozin upregulated the expression of genes related to bile acid metabolism in NCD only. Both groups showed a reduction in cholesterol ester, a major component of LDL cholesterol, in liver. Our results suggest that the efficacy of SGLT2i is attenuated under LCD, and that differences in liver metabolism between NCD and LCD under dapagliflozin treatment contribute to this outcome.
The Effect of Nutritional Transition on the Differentiation of Bone Marrow Stem Cells and the Therapeutic Effect of GLP-1

WENFANG XIA, LULU CHEN, QING ZHANG, ZHONGXING JIANG, HUANCHAO ZHU, JIE HUANG, WANGZHI HAN, YAN YANG, TAO ZHAO, XIAOHAN GUO, QIANG WANG, WANGFANG MA, SIHAN XU, ZHIHAI ZHANG, YUANYANG WANG, MIN JIA, XUN WANG, HUI JIANG, JIAN QIANG, JIAQiang ZHENG, WU ZHANG, HUIJIN WANG, JIANGCHENG LI

Background: Catch up growth is associated with glucose and lipid metabolism disorders, that can lead to osteoporosis and related fractures. Glucagon-like peptide-1 receptor agonists, such as liraglutide, exert an anabolic effect on bone in insulin resistant mice, but the mechanism for the action remains unclear. We established an animal model of catch-up growth to explore the actions of GLP-1 on bone mass and structure.

Methods: Thirty male C57BL/6 mice were randomly divided into the normal diet (ND, n=10), the catch-up growth model (RH, n=10) and the catch-up growth model + GLP-1 (RH+GLP-1, n=10) groups. Liraglutide was subcutaneously administered (200µg/kg, twice a day, for four weeks). After killing, tibia and fibula were removed for bone histomorphometry, bilateral femoral bone marrow mesenchymal stem cells were collected to evaluate their differentiation ability.

Results: GLP-1 administration decreased weight of visceral fat tissue, body weight, ratio between them, and blood lipids of the RH group. GLP-1 decreased triglyceride levels, and fatty acids in the liver, visceral fat tissue, subcutaneous fat tissue and skeletal muscle tissue. Compared to the ND group, GLP-1 secretion decreased in the RH group, but noticeably increased after GLP-1 administration. The areas under curves of intraperitoneal glucose tolerance test and insulin tolerance test and HOMA-IR in RH+GLP-1 group significantly declined. GLP-1 reversed deteriorated tibial and fibular bone structure in RH mice and induced osteoblastic differentiation.

Conclusion: Decreased ability of osteoblastic/osteogenesis differentiation of MSCs in RH mice led to impaired bone formation and GLP-1 intervention reversed the damage and enhanced insulin sensitivity.

Supported By: National Natural Science Foundation of China (81700649); Natural Science Foundation of Hubei Province, China (2016CB2452) Fundamental Research Funds for the Central Universities (016050024)
Angiogenesis-Inducing Enzyme 2 Deficiency Increases Translocation of Gut Bacteria by Depletion of Bone Marrow-Derived Circulating Angiogenic Cells

YAJIAN DUAN, DONGNI FENG, ELENI BELI, SERGIO LI CALZI, ANA LEDA F. LUNGO-HINO, REGINA LAEMENELLA, JUSTIN N. WRIGHT, TROY A. MARKEL, ALEXANDER G. GUKHOV, MARIA B. GRANT, Indianapolis, IN; Birmingham, AL; Huntington, WA.

A healthy microbiome is central to good nutrition and efficient metabolism. To maintain vascular integrity. We tested the hypothesis that angiotensin-converting enzyme 2 (ACE2), the key enzyme in the vasoactive axis of renin-angiotensin system (RAS), acts to regulate the infiltration of bone marrow-derived CACs in the gut and to maintain gut-vascular integrity in diabetes and could influence the systemic translocation of pathogenic antigens from the gut.

Diabetic ACE2 knockout (ACE2-/y)C57Bl/6J mice (Akita) mice were examined at 9 months after the onset of diabetes and compared to age-matched controls. Beta diversity analysis of the gut microbiome revealed a distinct bacterial profile among the different genotypes (n=9-17 per group, p=0.002). The fecal samples from ACE2-/y-Akita group compared to Akita group were enriched with a great diversity of bacterial taxa that have been described to contribute to the pathogenesis of diabetes and showed increased activation of pediatric-glycan syntheses pathways by metatranscriptome analysis (n=9 per group, p=0.005). Flow cytometry analysis showed that loss of ACE2 led to reduced infiltration of bone marrow-derived CACs (CD45^+Fk-1^CD31^-) into the gut (n=8-14 per group, p<0.0001), with modifying levels of pro-inflammatory and immune cell phenotypes. The CAC depletion mediated by loss of ACE2 deficiency was associated with increased levels of gut bacteria in the blood as assessed by SourceTracker analysis (n=9 per group). These data suggested a loss of the protective arm of RAS contributes to the depletion of CACs and disruption of gut-vascular barrier that may promote bacterial translocation in diabetes.

Supported By: National Institutes of Health (R01DK126001, R01DY007739, R01HL10170, R01DK9)
Conclusion: levels of pro-inflammatory cytokines and chemokines sufficient to induce insulin resistance and metabolic dysfunction in muscle are most likely provided by non-myocyte sources.

Supported By: U.S. Department of Veterans Affairs

**1905-P**

**Cause of Hyperglycemia in Postmenopausal Underweight Women With Impaired Glucose Tolerance**

RURIKO SUZUKI, YOSHIFUMI TAMURA, YUKI SOMEYA, HIDEYOSHI KAGA, DAISUKE SUGIMO, SATOSHI KADOWA, SADRI KAEKI, KAGUMI TAKENO, TAKASHI FUNAYAMA, YASUSHI KO FURUKAWA, JUNKO SATO, RYUZO KAWAMORI, HIROTAKA WATADA, TOKYO, Japan, Izunokuni, Japan

Japanese women have substantially lower BMI than women in other developed countries and the prevalence of overweight (BMI>18.5 kg/m²) in them is currently 23.7%. Interestingly, Japanese underweight women showed 2-3 times higher risk for type 2 diabetes compared with normal weight (BMI=18.5-22 kg/m²). A previous study reported that the hyperglycemia in obese impaired glucose tolerance (IGT) subjects was primarily elicited by reduced suppression of endogenous glucose production (EGP); however, cause of hyperglycemia in underweight women with IGT has not been elucidated. To clarify the role of EGP, rate of glucose disappearance (Rd) and rate of glucose appearance of oral glucose load (Ra-Oral) on hyperglycemia in underweight women with IGT, we recruited postmenopausal underweight women with NGT (n=4) and IGT (n=9). Glucose kinetics was assessed by oral glucose tolerance test (OGTT) with dual tracer (U-[13C]-glucose orally and 5,5-d2-TH2-glucose intravenously). Age, BMI, and percent body fat were comparable between NGT group and IGT group. IGT group showed lower area under the curve (AUC) of Rd compared with NGT group (129±20 vs. 189±370 mg/kg-fat free mass (FFM), P<0.05) during the first 2 hours of OGTT. Consistently, amount of disappeared glucose during the first 2 hours, mainly reflecting muscle glucose uptake, was 17.6g lower in IGT group compared with NGT group (39.8±9.5 vs. 57.4±14.4 g, P<0.05). In contrast, AUC-E GP and AUC-Ra-Oral were comparable between the groups. AUC-insulin during OGTT was lower in IGT group compared with in NGT group (623±8 vs. 4.6±0.9 U/min/m², P<0.01), and it was significantly correlated to AUC-Rd (r=0.70, P<0.01).

In conclusion, the present study suggested that main cause of hyperglycemia in underweight women with IGT was decreased Rd. In addition, decreased insulin secretion may partly contribute to the decreased Rd in those IGT subjects.

**1906-P**

**Heart-Specific Overexpression of HMGC-CoA Synthase 2 Induces Mitochondrial Stress—Adaptation via the ATP4 Pathway**

YASUO ZENIMARU, JINYA SUZUKI, TAKAHIRO NAKAYA, KAYA YAMADA, MAI ICHIKAWA, SATUSKI SATO, MICHIKO IMAMAGA, FREDRICK B. KRAEMER, TADASHI KONOSHITA, TAMOTSU ISHIUKA, FUKUJI, Japan, Stanford, CA

The liver is the central organ for ketone body production, and HMGC-CoA synthase2 (HMGCSC2) is a rate-limiting enzyme involved in this process. We reported that fasting markedly increased mRNA expression of HMGCSC2 in mouse heart, whereas its protein expression was faint and increased only marginally with fasting. To clarify the pathophysiological role of HMGCSC2 in the heart, we generated transgenic (Tg) mice with heart-specific HMGCSC2 overexpression and analyzed the effects on metabolic status in the myocardium. Plasma concentrations of 3-hydroxybutyrate (3HB), glucose and free fatty acids were comparable between Tg and wild type (WT) mice, whereas the cardiac 3HB content in Tg mice was increased 10-fold (fed state) or 2-fold (24h-fasted state) over that of WT mice. Confocal microscopy demonstrated that the HMGCSC2 protein co-localized with a mitochondrial protein, ATPSA, in cardiomyocytes of Tg mice. Transmission electron microscopy showed many swollen mitochondria, some of which contained vacuole-like vesicles and decreased cristae in Tg hearts, and ultrastructural showed impaired cristalline function. Microarray gene expression analysis revealed that approximately 800 genes were altered <2-fold in Tg hearts compared with WT hearts. Among the altered genes, ATP4 and its target genes, including PHGDH, MTHFD2 and ASNS which promote glutathione production, were upregulated in Tg hearts. Consistent with this result, a metabolome analysis performed by capillary electrophoresis-mass spectrometry demonstrated that glutathione was increased in Tg hearts, suggesting an adaptation to mitochondrial stress. In addition, 3 branch-chain amino acids were increased in Tg hearts compared with WT hearts. These results indicate that myocardial HMGCSC2 can produce ketone bodies in mitochondria, leading to mitochondrial stress and cardiac dysfunction. The limited induction of HMGCSC2 protein upon fasting might constitute a protective mechanism for cardiomyocytes.
COEN, RICK B. VEGA, BRET H. GOODPASTER,
Orlando
group completed a supervised exercise program. Mitochondrial respiratory

tion-induced weight loss.

vs. POST: 79.6±19.3 pmol/s*mg) after the exercise training.

the WLEX group presented an increased maximal OXPHOS (PRE: 50.7±10.1

CON and CRWL groups after the 6-month intervention (p>0.05), subjects in

IS was determined by hyperinsulinemic euglycemic clamps.

phorylation (OXPHOS), and maximal uncoupled respiration were evaluated.

Korean Diabetes Association; Bucheon St. Mary's Hospital

ment can effectively alter protein expression in the gastrocnemius muscle

γ

the phosphorylation levels of 5'-AMP-activated protein kinase, sirtuin 1, and

OLETF-G rats (P < 0.05). Insulin glargine treatment significantly increased

insulin-like growth factor-I levels were increased, in the skeletal muscle of

myokines (interleukin [IL]-6, IL-15, fibronectin type III domain containing 5

higher, respectively, in OLETF-G compared with OLETF-C rats. Activation of

heavy chain (MHC) isoforms were altered in gastrocnemius muscle of

C), and the area under the curve was significantly decreased for OLETF-G

was assessed by real-time PCR.

was detected by Western blot analysis, and muscle fiber type composition

in the skeletal muscle of Otsuka Long-Evans Tokushima Fatty (OLETF) rats.

Supported By: National Institutes of Health/National Institute on Aging

Restricted ‑Induced Weight Loss to Improve Insulin Sensitivity

Exercise Is Required to Improve Mitochondrial Respiratory Capac ‑

1907-P

1908-P

2012R1A4A1042272; Korean Diabetes Association; Bucheon St. Mary's Hospital

Supported By: Korean National Research Foundation (2012R1A1A1014272); TETSUYA HOSODA, WATARU OGAWA, Koji, Japan, Kodaira, Japan, New York, NY

Background: Evidence suggests that diabetes is a promoting factor of sarcopenia. Mechanism how the condition accelerates the development of sarcopenia remains ambiguous. Results: In streptozotocin (STZ)-induced diabetic mice, skeletal muscle mass was decreased by ~15% within 21 days after the STZ treatment. The protein abundance of transcription factor KLF15 as well as the mRNA abundance of proteins related to muscle atrophy (Foxo3a, Atrogin1 and Murtfh) were elevated whereas the mRNA of KLF15 was unaltered in skeletal muscle of STZ-diabetic mice. Decrease in skeletal muscle mass and increase in the mRNA abundance of muscle atrophy-related proteins triggered by STZ-induced diabetes were prevented in muscle-specific KLF15 deficient mice suggesting that KLF15 plays a key role in diabetes-induced muscle atrophy. Treatment of C2C12 cells with high concentration of glucose (25 mmol/l) decreased the ubiquitination of and increased the protein abundance of KLF15. The E3 ubiquitin ligase WWP1 was found to be downregulated in skeletal muscle and increased the skeletal muscle mass of these mice. KLF15 Pathway

Coadministration of GLP-1 and Y2R Receptor Agonists Synergize to Promote Muscle Glucose Uptake and Induce Diabetic Remission

BRANDON BOLON, VICTOR G. HOWARD, MICHELLE BEATON, SARAH WILL, STEPHANIE OLDHAM, JAMES TREVASKIS, CHRISTOPHER J. RHODES, JOE GRIMSBY, Galbcreburg MD

One proposed mechanism for the effects of bariatric surgery is the enhanced postprandial release of enteroendocrine L-cell hormones, such as PYY and GLP-1. Four week co-administration of Fc-conjugated GLP-1R and Y2R-selective agonists induced weight loss, reduced %HbA1c, and improved glucose tolerance in IDO and KS db/db mice compared to vehicle or monotherapy control groups. To assess the impact of this combination on glucose control, a hyperinsulinemic/euglycemic clamp was performed in KS db/db mice following two week treatment with vehicle or co-administration of GLP-1/Y2R agonists. A vehicle-treated group weight-matched to combination-treated mice was also assessed. Compared to KS db/db vehicle animals, combination-treated mice exhibited a 16-fold greater glucose infusion rate compared to only 4-fold in weight-matched controls. Glucose uptake was increased 4-fold in the skeletal muscle of combination-treated animals, but was unaltered in adipose or brain. Weight-matched controls did not exhibit increased glucose uptake in any tissue. To better characterize the mechanism of Fc-GLP-1/Fc-Y2R action on peripheral glucose metabolism, lean mice were acutely administered Fc-GLP-1 and/or Fc-Y2R, and then sacrificed to assess brain c-Fos activation. Compared to monotherapies, combination administration led to additive c-Fos activation in hindbrain regions. Strikingly, whereas monotherapy had no effect on the PVH, combination administration led to a synergistic 2-fold increase in c-Fos immunoactivity. These findings implicate a neuronal population in the PVH as a putative driver of the antidiabetic efficacy observed following co-administration of GLP-1R and Y2R selective peptides, and may represent a novel mechanism to improve insulin sensitivity and skeletal muscle glucose uptake.

Moderated Poster Discussion

1909-P

Promote Muscle Glucose Uptake and Induce Diabetic Remission

YU HIRATA, KAZUHIRO NOMURA, YOKO SENGU, MICHIOHI IMAMURA, SHIN'ICHI TAKEDA, YUKO OKADA, STEVEN J. BURDEN, TETSUYA HOSODA, WATARU OGAWA, Kobe, Japan, Kodaira, Japan, New York, NY

POSTERS

KLF15 Pathway

Hyperglycemia Promotes Muscle Atrophy through the WW1/PYY and GLP-1/Y2R-selective peptides, and may represent a novel mechanism to improve insulin sensitivity and skeletal muscle glucose uptake.

The aim of this study was to investigate the effect of 6-month diet-induced weight loss intervention with or without the addition of exercise training on skeletal muscle mitochondrial respiratory capacity and IS.

Methods: Forty-four older adults with obesity were randomized to one of the following 6-month intervention: Health education (CON: n=14, age=70±4 years, BMI=33±5 kg/m²), Diet induced weight-loss (DIWL: n=14, age=70±4 years, BMI=36±5 kg/m²), or Weight-loss and exercise (WLEX: n=16, age=66±3 years, BMI=37±5 kg/m²). CRWL and WLEX participants had a goal of 10% weight-loss through calorie restriction. Subjects in the WLEX group completed a supervised exercise program. Mitochondrial respiratory capacity of permeabilized myofibers from biopsies was evaluated by high-resolution respirometry. Complex I-II supported maximal oxidative phosphorylation (OXPHOS), and maximal uncoupled respiration were evaluated. IS was determined by hyperinsulinemic euglycemic clamps.

Results: IS improved in both CRWL (10.4%) and WLEX (50%) compared to CON (0.7%). However, while mitochondrial respiration was unchanged in the CON and CRWL groups after the 6-month intervention (p>0.05), subjects in the WLEX group presented an increased maximal OXPHOS (PRE: 50.7±10.1 vs. POST: 72.6±17.9 pmol/s*mg) and uncoupled respiration (PRE: 57.2±10.5 vs. POST: 79.6±19.3 pmol/s*mg) after the exercise training.

Conclusions: Despite weight loss and exercise both improving muscle sensitiv­­ity, exercise is required to improve mitochondrial respiratory capacity in skeletal muscle of older obese human subjects undergoing calorie restric­tion-induced weight loss.

Supported By: National Institutes of Health/National Institute on Aging (R01AG021961 to B.H.G.)
Exogenous Delta-Like 1 Homolog (DLK1)−Fc Treatment Attenuates Muscle Atrophy in Both Dexamethasone- and High-Fat Diet-Induced Obesity Mice Models


Skeletal muscle degeneration is accelerated in elderly patients with diabetes and the imbalance between muscle growth and wasting can lead to metabolic dysfunction. DLK1 is a member of the EGF-like family and essential for skeletal muscle development and regeneration. To identify whether exogenous DLK1 treatment can prevent muscle wasting, we assessed muscle mass as well as muscle differentiation and atrophy markers in two different models: dexamethasone and high fat diet (HFD)-induced obesity mouse models (n=7-8 per each group). In the dexamethasome model, mice were divided into (1) control, (2) dexamethasone treatment (1mg/Kg, 2 weeks), and (3) DLK1 (0.8mg/Kg, 2 weeks) and dexamethasome treatment groups. In the HFD model, mice were divided into (1) control, (2) HFD (50% calories from fat, 8 weeks), and (3) HFD with DLK1 treatment (0.8mg/Kg, 8 weeks) groups. The expressions of genes related to muscle differentiation and atrophy were determined using RT-PCR. We observed that dexamethasone reduced muscle mass and markedly increased atrophy markers including atrogin-1 and mrf-1. DLK1 treatment attenuated these degenerative changes. Furthermore, the level of myostatin, which inhibits muscle cell growth, was reduced in DLK1 treatment group compared to dexamethasome group. Additionally, compared to HFD group, DLK1 inhibited muscle atrophy by increasing the differentiation marker: myoD, and decreasing the atrophy markers: myostatin, atrogin-1, and mrf-1. Taken together, these results suggest that DLK1 attenuates both dexamethasone and HFD-induced muscle atrophy in mice by suppressing the downstream signaling of myostatin/atrogin-1/mrf-1 pathway. The increased expression of myd8 indicates that DLK1 treatment could also improve the quality of muscle formation. Our study implies that DLK1 could be a promising candidate in the treatment of aging or diabetes-related sarcopenia, characterized by muscle atrophy and dysfunction. Supported By: Yonsei University College of Medicine

Iron Overload Plays an Important Role in ER Stress-Induced Insulin Resistance in Human Skeletal Muscle Cells

Kwanwoo Lee, Rihua Cui, Dae Jung Kim, Sung Eun Choi, Seong Hun Jang, Hae Jin Kim, Seoul, Republic of Korea, Seoul, Republic of Korea

Aim: In this study, we investigated the relationship and molecular mechanisms between iron-overload and ER stress-induced insulin resistance in human skeletal muscle cells. Methods: Intracellular iron was measured using calcein AM. Iron metabolism-related genes were analyzed by immunoblotting and PCR. The study was conducted using iron supplementation, which was achieved by palmitate, FeSO4 and FeCl3 administration, and iron reduction, which occurred by DFO, DS and Bapta-AM administration, and knockdown of TfR1 or IRF2 genes, to investigate the effects of iron metabolism on insulin sensitivity in HSMMS. Intracellular calcium was detected using Fluo-3/AM staining. TR1 internalization regulated by calcium was detected by GFP-labelled transferrin.

Results: Endoplasmic reticulum stress by tunicamycin, thapsigargin, or palmitate evoked insulin resistance and simultaneously increased intracellular iron. Iron chelator, DFO, dramatically prevented ER-stress induced insulin resistance and iron donor impaired insulin sensitivity in vitro and in vivo through activation of JNK. Among several iron metabolism-related genes, TfR1 plays a predominant role for maintaining iron homeostasis in HSMMS. Treatment of ER-stress induced proliferatively regulated translocation of TfR1 by intracellular calcium, but protein levels of TfR1 did not change. Iron reduction, by adding iron chelator, calcium chelator, or knockdown of TfR1 or IRF2, dramatically prevented ER-stress-induced insulin resistance through the reduction of iron-overload.

Conclusions/Interpretation: The current study shows ER-stress induced evoked insulin resistance through iron overload. Reduction of intracellular iron, by iron chelator, significantly prevents insulin resistance. Therefore, attempts to block iron overload might be a strategy for preventing insulin resistance and diabetes.

Clinical Significance of Insulin Sensitivity in Adipose Tissue in Apparently Healthy Nonobese Men

Daitsuke Sugimoto, Yoshihumi Tamura, Kageumi Takeno, Hideyo-Shi Kaga, Yuki Somaeya, Ruriko Suzuki, Satoshi Kadowaki, Takaishi Funayama, Yashiko Furukawa, Ryuzo Kawamori, Hirotsuka Watada, Tokyo, Japan

Increased plasma free fatty acid (FFA) level is reported to be an important cause of obesity-associated insulin resistance in muscle and liver. Increased plasma FFA level in obesity is induced by insufficient suppression of plasma FFA by insulin and this is defined as impaired insulin sensitivity in adipose tissue (Adipo-IS). However, significance of impaired Adipo-IS in non-obese healthy subjects is totally unknown. To clarify this, we studied 49 non-obese (BMI: 25kg/m2) apparently healthy Japanese men without any cardiovascular risk factors (mean age, 40.2±5.3 y.o, mean BMI, 23.1±1.0 kg/m2). We performed a 2-step hyperinsulinemic euglycemic clamp test (10 and 20 mU/m2 per min, 3h for each) to measure insulin sensitivity in muscle and liver. In addition, plasma FFA levels were also measured at fasting and 2nd step during the glucose clamp. Ectopic fat tissues in muscle and liver and visceral fat area (VFA) were measured by 1H-MRS and MRI, respectively. The plasma FFA level was decreased from 530.6±139.1µEq/l to 62.4±64.2µEq/l during hyperinsulinemic euglycemic clamp. Thus, the mean Adipo-IS, defined as %FFA suppression during glucose clamp, was 88.8±10.3%; however, there was a large individual variations in Adipo-IS. Interestingly, Adipo-IS was positively correlated to insulin sensitivity in muscle (r=0.50, p<0.001) and liver (r=0.44, p=0.002) and negatively correlated to fasting plasma glucose (r=-0.33, p=0.019) and fasting insulin concentration (r=-0.46, p=0.001). In contrast, Adipo-IS had no significant correlation with fasting FFA, VFA, adipokines (adiponectin, TNF-alpha, MCP-1 and IL-6), CRP and ectopic fat in muscle and liver, respectively. These data suggested that moderately impaired Adipo-IS may be early functional abnormality in adipose tissue occurred in apparently healthy non-obese men. The impaired Adipo-IS may contribute to slightly reduced insulin sensitivity in muscle and liver and elevated plasma glucose level.
Mitochondrial Adaptation in Insulin Resistant Human Skeletal Muscle

CHRISTOPHER L. AXELROD, CARAN E. FEALY, ANNY MULYA, EMILY HUANG, HISASHI FUKUDA, BARTOLOME BURGUESA, CHARLES L. HOFFEL, JOHN P. KIRWAN, Baron Rouge, LA, Cleveland, OH

Introduction: The integrity, morphology, structure and functionality of skeletal muscle mitochondria in patients with type 2 diabetes (T2D) is heavily disputed. Thus, the purpose of this investigation was to characterize mitochondrial phenotypes across the insulin resistance spectrum.

Methods: 30 sedentary adults aged 19-55 were grouped as lean (BMI 21±0.6, N=13), obese (BMI 32±0.9, N=12), or T2D (BMI 33±2.5, N=5) based on oral glucose tolerance tests and body mass index (BMI). All subjects completed a 3-day, inpatient stay consisting of cardio-metabolic testing, body composition analysis and a hyperinsulinemic-euglycemic clamp study. On the day of the clamp, muscle specimens were obtained basally and under insulin-stimulated conditions. Mitochondrial membrane potential (ΔΨm) was measured by confocal microscopy using the cationic fluorophore TMRM. Oxidative phosphorylation (OXPHOS) was assessed in permeabilized fibers via high resolution respirometry (Oroboros Oxygraph-2k). Muscle mitochondrial ultrastructure and content were determined by transmission electron microscopy (TEM) of fixed muscle sections.

Results: There was a significant, step-wise decrease in insulin-stimulated glucose uptake across the metabolic spectrum (P<0.001). No differences in resting ΔΨm were observed, however, insulin stimulation depolarized ΔΨm in all groups (P<0.05). Those with T2D exhibited increased basal complex III (P<0.05) and IV (P<0.05) activity vs. lean and obese controls. Furthermore, obese controls and T2D displayed augmented complex IV responsiveness to insulin stimulation (P<0.01). Threshold analysis of muscle sections revealed a progressive loss of mitochondrial content, as well as accumulation of lipid droplets across the metabolic spectrum (P<0.05).

Conclusion: Collectively, these findings provide direct evidence of mitochondrial impairment in insulin resistant and diabetic skeletal muscle.

Supported By: National Institute of Diabetes and Digestive and Kidney Diseases

Effects of Diet/Exercise and Pioglitazone on the Association between Fitness and Intramyocellular FFA Trafficking

SAMYAH SHADID, ENDOCRINE RESEARCH UNIT, MAYO CLINIC, MICHAEL D. JENSEN, Ghent, Belgium; Rochester, MN

Background: Intramyocellular (im) triglycerides (TG) are increased in athletes, but also insulin resistant (IR) adults. To elucidate this discrepancy, we studied FFA storage in imTG and im oleoyl-carnitine (OC) concentrations in IR humans pre and post 2 months of insulin sensitization (IS) in the context of fitness (VO2max).

Methods: 39 adults (BMI 28-36 kg/m2) were given a diet/exercise program (DE, 11.7 ± 3.2 kg weight loss) or 30 min/day pioglitazone (PI) for 19 weeks. Blood and muscle samples were taken before and after a 6 hour (U-13C)oleate infusion with either a euglycemic, hyperinsulinemic clamp (n=20) or saline infusion. Plasma oleate storage in imTG (mmol FFA/g muscle) was calculated.

Results: Quantative IS was similar in DE and PI groups. VO2max increased post DE (4 ± 1 to 4.6 ± 2 ml/kg/min); however, VO2max did not correlate with the A Dalek storage in imTG. Following IS, VO2max correlated with imOC (n=0.48*); the latter was true for men (m) (n=0.89*), but not women (n=0.32), and for DE (m: n=0.97*) but not PI (m: n=0.70, p=0.18). A VO2max correlated with AmOC (m: n=0.92*, f: n=0.57), both post WL (n=0.91*) and PI (n=0.96*). Summary: In IR adults, IS influences the associations between fitness and markers of imFFA oxidation and storage in imTG during hyperinsulinemia. These relationships are more apparent in men and exacerbated post-IS.

Conclusion: Fitness in men regulates imFFA trafficking towards storage and oxidation. *p<0.05; †p<NS.

Supported By: National Institutes of Health

Mitochondrial Adaptation in Insulin Resistant Human Skeletal Muscle

1916-P

Age-Related Attenuation of Aerobic Exercise Training Adaptation in 24-Week Old Rats

REBECCA L SCAILO, GRAHAME F EVANS, SARA E HULL, LESLIE KNAUB, LORI A. WALKER, JANE E. REUSCH, Aurora, CO; Durham, NC; Denver CO

Studies of age related declines in health and function often focus on the end of the lifespan. However, chronic diseases such as type 2 diabetes (T2D) develop in middle age. The purpose of this study was to determine the effect of aerobic exercise training on vascular and skeletal muscle responses in mature rats. We hypothesized that mature rats would have attenuated adaptations to exercise training. Young (Y; 12-week old; n = 8) and mature (M; 24-week old; n = 8) male Wistar rats performed 3 weeks of treadmill running (Ex) or remained sedentary (S). After this time period, insulin and glucose uptake across the metabolic spectrum (P<0.001). No differences in resting ΔΨm were observed, however, insulin stimulation depolarized ΔΨm in all groups (P<0.05). Those with T2D exhibited increased basal complex III (P<0.05) and IV (P<0.05) activity vs. lean and obese controls. Furthermore, obese controls and T2D displayed augmented complex IV responsiveness to insulin stimulation (P<0.01). Threshold analysis of muscle sections revealed a progressive loss of mitochondrial content, as well as accumulation of lipid droplets across the metabolic spectrum (P<0.05).

Conclusion: Collectively, these findings provide direct evidence of mitochondrial impairment in insulin resistant and diabetic skeletal muscle.

Supported By: National Institute of Diabetes and Digestive and Kidney Diseases

1917-P

Skeletal Muscle Clock Is Essential for Nutrient-Sensing and Inter-organ Metabolic Fuel Partitioning

KE MA, SOMIK CHATTERJEE, HONGSHAN YIN, Duarte, CA; Houston, TX; Shijiazhuang, China

The circadian clock exerts temporal control in metabolism and its disruption leads to the development of diabetes and obesity. Tissue-intrinsic clock circuits are integral components of global metabolic homeostasis, although how they sense nutrient signals to orchestrate metabolic flux is not clear. Skeletal muscle is major site for metabolic substrate oxidation, and its utilization of glucose and fatty acid depends on availability of nutrients accompanying feeding-fasting transitions. Interestingly, nearly 30% of rhythmic transcripts in skeletal muscle belongs to metabolism. By generating a mouse model with myocyte-selective ablation of the clock transcription activator Bmal1, here we show that cell-autonomous muscle clock plays an essential role in coordinating nutrient utilization with feeding-fasting induced cycles. Bmal1 in skeletal muscle was robustly induced by feeding, and its loss markedly impaired feeding-induced switch to glucose metabolism from fatty acid utilization. As a result, Bmal1-deficient muscle displays nearly 50% reduction of glucose oxidation whereas fatty acid oxidation was enhanced, resembling a constant fasting state. This metabolic shift was accompanied by muscle fiber type switching to an oxidative phenotype, and led to a remarkable resistance to hepatic lipid accumulation induced by prolonged fasting or high-fat diet feeding. In contrast, systemic fasting glucose levels in muscle Bmal1−/− mice were elevated, which is due to a failure of suppressing hepatic glucose output as revealed by hyperinsulinemic-euglycemic glucose clamp study. Collectively, our results reveal a novel function of the Bmal1-driven muscle clock as a key metabolic sensor that coordinates metabolic fuel oxidation with oscillatory nutrient availability in fasting-feeding cycles. This temporal mechanism in orchestrating global nutrient flux may contribute to metabolic abnormalities induced by circadian misalignment.

Supported By: American Heart Association (17GRN33330012); National Institutes of Health (R01DK112794-01A1)

1918-P

Natriuretic Peptide Deficiency Causes Skeletal Muscle Insulin Resistance in Mice

CEDRIC MORGO, Toulouse, France

Cardiac natriuretic peptides (NP) have been shown to control energy homeostasis. Epidemiological studies have shown that low level of plasma NP predict future development of type 2 diabetes (T2D). We have also observed a reduced expression of the biologically active NP receptor GCA of about 50% in metabolic tissues of obese humans and mice. The purpose of this study

1919-P

Integrated Physiology—MUSCLE

POSTERS

ADA-Supported Research
Moderated Poster Discussion
was to demonstrate that NP deficiency causes T2D in mice. GCA+/+- and atrial NP/-/- (ANP) mice and their wild type (WT) littermates were studied under normal Chow and highfat diet for 12 weeks. GCA+/+- and ANP/-/- mice exhibit signs of systemic insulin resistance and glucose intolerance when compared to their WT littermates. This metabolic phenotype is accompanied by skeletal muscle insulin resistance and reduced lipid oxidative capacity, without noticeable changes in inflammatory profile of liver and adipose tissues. Interestingly, we observed elevated levels of lipotrophic lipids in skeletal muscle along with reduced mitochondrial mass and respiratory chain complexes. Collectively, these data indicate that ANP/GCA deficiency causes T2D and that ANP contributes to long-term maintenance of insulin sensitivity.

Supported By: Allocation de Recherche SFD-Roche Diabetes Care

**INTEGRATED PHYSIOLOGY—MUSCLE**

**1922-P**

**Nfkb Regulation of Mitochondrial Function in Skeletal and Cardiac Muscle**

JOE VALENTINE, MENGYAO E. LI, NING ZHANG, STEVEN E. SHOELSON, NICOLE LAS MUSI, SAN ANTONIO, TX, BOSTON, MA

Nfib is a transcription factor that controls immune and inflammatory processes. In muscle, Nfib has been implicated in regulation of muscle mass/function, metabolism, and mitochondrial function. Yet, Nfib’s role in aging-related changes to skeletal muscle and heart remains less defined. To investigate the role of Nfib in aging skeletal muscle and heart, we studied a mouse model (MISR mice) with suppressed Nfib signaling in these tissues. Recently we found that these mice have exacerbated loss of skeletal muscle mass during aging. Here, we report that Nfib suppression caused reductions in skeletal muscle mass as early as 1 month of age. Aging per se (in WT mice) lead to a global downregulation of mitochondrial function (reduced respiration and enhanced reactive oxygen species production) and expression of mitochondrial biogenesis genes in skeletal muscle. Furthermore, suppression of Nfib signaling in skeletal muscle resulted in mitochondrial function defects in early life (4 months old), whereas in aged mice (30-33 months old) it had the opposite effect. Contrary to findings in skeletal muscle, in the heart aging increased mitochondrial respiration and reactive oxygen species production (in WT mice) and Nfib suppression protected against the aging related changes to reactive oxygen species production. We conclude that suppression of the canonical Nfib pathway has antagonistic pleiotropic effects (detrimental in early life and advantageous in aging animals) on mitochondrial function in skeletal muscle, but is beneficial throughout the lifespan in the heart. Furthermore, canonical Nfib signaling regulates muscle development and cellular metabolism at the transcriptional and functional levels.

**1923-P**

**Diabetes and High-Fat Diet Induce Different Pathologies in Mouse Skeletal Muscle Extracellular Matrix**

SERGIO F. MARTINEZ-HUENCHULLAN, LINDA A. BAN, ANH TAO, SURYA S. SUTANTO, CHARMAINE TAM, SUSAN MCLENNAN, STEPHEN M. TWIGG, SYDNEY, AUSTRALIA

Whether obesity and diabetes (DM) similarly affect composition and function of skeletal muscle extracellular matrix (ECM) has not been resolved. This study examines the effects of long-term high-fat diet (HFD) and rodent skeletal muscle ECM were addressed. Five week old C57BL/6 male mice were randomly allocated to standard chow (control; n=26) or HFD (45% kcal fat; n=25). After 15 weeks Chow and HFD mice were rendered diabetic (by low dose STZ, 65mg/kg, i.p.) (DM, n=14; HFD+DM, n=14), nondiabetic mice acted as controls. Mice were euthanased after 30 weeks and plasma and quadriceps muscle were collected for analysis. Body weight and plasma insulin expectedly decreased with DM induction and increased with HFD (all p<0.05). High glucose occurred only in DM mice (~14 mM; p<0.05), whereas only HFD increased muscle triglyceride (p<0.05). Both conditions induced a decrease in quadriceps weight and in grip strength performance (p<0.05). Quadriiceps of DM mice showed increased CTGF/CCN2 (1.5 fold; p<0.05), TIMP-1 (2 fold; p<0.05), collagen-I (3 fold; p<0.05), IV (2 fold; p<0.05), and −VI (2 fold; p<0.05) protein. In contrast, HFD induced a downregulation of CTGF/CCN2 (0.6 fold; p<0.05), MMP-1 (0.6 fold; p<0.05), and TIMP-2 (0.4 fold; p<0.05). In DM mice quadriceps centralised nuclei (p<0.05) and caspase 3 (protein; 1.5 fold; p<0.05) were increased, whereas caspase 3 was decreased in HFD (0.5 fold; p<0.05). Moreover, HFD induced a downregulation of ubiquitin ligase atrogen-1 protein (0.5 fold; p<0.05) and mRNA levels of serine/threonine kinase 70 (p0.7 fold; p<0.05). Notably, no greater dysregulation of the muscle changes observed with DM alone or with HFD alone, was seen in HFD+DM mice. These data suggest that DM and HFD differentially affect skeletal muscle ECM: DM promotes a pro-fibrotic profile with signs of muscle damage, and HFD impairs regulatory protein turnover pathways, each inducing muscle dysfunction.

Supported By: National Health and Medical Research Council of Australia; National Commission for Scientific and Technological Research of Chile
50-60% decrease in state 3 respiration measured using substrates support-
(number of repetitions: 15 ± 0.6 vs. 20 ± 0.3, p = 0.01). They also had a
not different, but FPLD individuals had earlier fatigue during chest press
content, and higher lean mass. Peak leg press and chest press force were
supporting carbohydrate or lipid-based respiration. Insulin Sensitivity Index
ses were obtained prior to and following a high fat (40%) mixed-meal. Oxy-
recumbent leg press and seated chest press. Vastus lateralis muscle biop-
6 individuals with FPLD and 6 matched controls.
therefore systematically investigated muscle and mitochondrial function in
Affected individuals also display striking skeletal muscle hypertrophy, but
caracterized by post-natal fat loss leading to severe insulin resistance.

JOHN PORT, MARCELLO C. LAURENTI, CLAUDIO COBELLI, K. SREEKUMARAN
Diminished Mitochondrial Fatty Acid Oxidation
individuals with Familial Partial Lipodystrophy Is Associated with
Skeletal Muscle Dysfunction and Metabolic Abnormalities in Indi ‑
1925‑P
Skeletal Muscle Dysfunction and Metabolic Abnormalities in Indi –
with Familial Partial Lipodystrophy Is Associated with
Diminished Mitochondrial Fatty Acid Oxidation
VINAYA SIMHA, IMI R. LANZA, NATHAN LEBRASSEUR, KATHERINE KLAUS,
JOHN PORT, MARCELLO C. LAURENTI, CLAUDIO COBELLI, K. SREEKUMARAN
NAIR, Rochester, MN, Albuuzzano, Italy, Padova, Italy
Background: Familial Partial Lipodystrophy, Dunnigan variety (FPLD) is
characterized by post-natal fat loss leading to severe insulin resistance. 
Affected individuals also display striking skeletal muscle hypertrophy, but
there is limited information on muscle function and energy metabolism. We
therefore systematically investigated muscle and mitochondrial function in
6 individuals with FPLD and 6 matched controls.
Methods: Body composition and intramyocellular lipid content (IMCL) were
assessed by DEXA and magnetic resonance spectroscopy, respect-
ively. Maximal voluntary strength and fatigue were assessed for both
recumbent leg press and seated chest press. Vastus lateralis muscle biop-
sies were obtained prior to and following a high fat (40%) mixed-meal. Oxygen
consumption in isolated mitochondria was measured using substrates
supporting carbohydrate or lipid-based respiration. Insulin Sensitivity Index
(SI) was calculated by minimal modelling.
Results: Individuals with FPLD had significantly lower SI, lower body fat
content, and higher lean mass. Peak leg press and chest press force were
not different, but FPLD individual fatigue during chest press (number of repetitions: 15 ± 0.6 vs. 20 ± 0.3, p = 0.01). They also had a
50-60% decrease in state 3 respiration measured using substrates support-
ing lipid-based respiration (p = 0.04). Further, mitochondrial oxidative capa-
city showed a strong correlation with muscle fatigue (r = 0.76, p = 0.003), and
inversely correlated with fasting and post-prandial lipemia and measures of
insulin resistance. Conclusion: Individuals with FPLD have higher lean body mass and lower insulin sensitivity. Despite preserved peak muscle strength, they demonstr-
ated earlier muscle fatigue. Decreased mitochondrial fatty acid oxidative
capacity, likely related to elevated IMCL, may contribute to muscular and
metabolic abnormalities. Supported By: Mayo Clinic

1926‑P
Skeletal Muscle Lipid Composition Parallels Clinical Phenotype
Extremes
LISA S. CHOW, DOUGLAS G. MASHEK, TYLER BOSCH, ANNE BANTILE, MAI FET-
TERSON, DONALD R. DENGEL, MICHAEL D. JENSEN, Minneapolis, MN, Roches-
ter, MN
Intramyocellular lipid (IMCL) is generally associated with insulin resis-
tance and lipotoxicity. However, the “athlete’s paradox” is well documented,
where IMCL levels are similar between athletes and patients with type 2
diabetes despite discrepant levels of insulin sensitivity. Differences in mus-
cle lipid metabolites between aerobically trained, lean, insulin‑sensitive (LT)
vs. sedentary, overweight/obese, insulin‑resistant (OIR) individuals remain
insufficiently characterized and may help to explain the “athlete’s paradox.”
LT [n=14: 50% females, 28.5±1.6 years (Means±SE)] and OIR [n=24: 79% 
females, 29.6±1.8 years] subjects each provided 2 muscle biopsies from the
vastus lateralis (bilateral, 6 hours apart, <±48 hours after last exercise, ≥8
fasting, overnight admission prior to biopsy) for mass spectrometry analy-
sis. At a separate visit, insulin sensitivity was quantified by a hyperinsul-
emic-euglycemic clamp (mg glucose/kg FFM/min). As the sequential biopsy
results were not significantly different, the results were averaged for each
subject. Compared with the OIR group, the LT group had lower BMI [22.3±0.5
vs. 30.2±1.2 kg/m²; p<0.01], higher fitness (VO2max:53.4±2.2 vs. 26.7±1.1
ml/kg/min; p<0.01), and higher insulin sensitivity (M-value: 17±0.7 vs.
8±0.5, p<0.01). Muscle triglycerides in the LT group were lower (mmol/mg
muscle) in oleic acid (3.2±0.6 vs. 6.0±1.0, p<0.02) and palmitic acid (1.5±0.2
vs. 3.1±0.5, p<0.01) than the OIR group. Diacylglycerol (DAG) and palmitoyl-
carnitine concentrations were not significantly different. Only in the LT
group, palmitoylcarnitine correlated with the following: oleic acid (r=0.73, 
p<0.01), palmitic acid (r=0.73, p<0.01) and DAG (diplamidic acid: r=0.53, 
p<0.03, palmitate:diacete: r=0.51, p<0.04). These findings suggest that either incom-
plete muscle lipid oxidation or increased acylcarnitine generation is present in
the OIR group, thus warranting further research on training effects on
muscle lipid turnover. Supported By: National Institutes of Health

1927‑P
Febuxostat Improves Insulin Resistance in the Skeletal Muscle In
Vitro and In Vivo
CHHIREI T. MORIYA, HIRAKO SATOH, HIROTAKA WATADA, Tokyo, Japan
Hyperuricemia is closely associated with various metabolic disorders
such as diabetes, hypertension, dyslipidemia, and cardiovascular diseases.
Xanthine oxidoreductase (XOR) is a key enzyme that catalyzes the conversion
of uric acid. Febuxostat is an orally-active, potent, non-purine, selective XOR
inhibitor. However, the effect of febuxostat on glucose and insulin metabo-
lism has not been fully elucidated. Therefore, we investigated the effect of
febuxostat on insulin sensitivity in male Wistar rats. Insulin sensitivity
was evaluated by the hyperinsulinemic-euglycemic glucose clamp studies
(at 25 µU/kg/min insulin infusion rate) after an 8-hour fast. Male Wistar rats
were 60% high fat diet containing with either febuxostat (~4 mg/kg/day) or
not, for 4 weeks. The glucose infusion rate and insulin-stimulated glucose
disposal rate were significantly increased by 12% and 17%, respectively. But
hepatic glucose output was no significant change between two groups. Con-
sistent with the clamp data, the insulin-stimulated phosphorylation of Akt and
AMPK were significantly increased by 90% and 53%, respectively, only in
skeletal muscle of febuxostat treated rats. Next, to investigate whether this
effect is direct or indirect, we examined the effect of febuxostat in the
differentiated C2C12 cells. The treatment of 10 µM febuxostat for 48
hours significantly increased the phosphorylation of Akt and AMPK by 65%
and 43% (P=0.028) in the differentiated C2C12 cells, respectively. These results
suggest that this effect of febuxostat is direct.
In conclusion, these findings indicate the possibility that febuxostat acts
directly on the skeletal muscle and improves insulin resistance.
Supported By: National Institutes of Health

Supported By: National Institutes of Health (R01DK087269)
Mechanism Underlying the Biphasic Effect of ADP on Succinate-Energized Muscle Mitochondrial Respiration
BRIAN FINK, LIRING YU, WILLIAM SIVITZ, Iowa City, IA
Recently, we reported a novel phenomenon involving basic mitochondrial physiology. When ADP was sequentially added to mouse skeletal muscle mitochondria energized by succinate (in the absence of rotenone, commonly used to block complex I), we found a biphasic (increasing then decreasing) respiratory dose-response to clamped concentrations of ADP. Here we studied the mechanism. First, we confirmed observations that oxaloacetate (OAA) inhibits succinate dehydrogenase (SDH) by assessing the activity of the extracted complex. OAA is known to be difficult to measure by mass spectrometry. Here we used a nuclear magnetic resonance method to assess OAA as well as malate and fumarate in mitochondria respiring on succinate. When isolated muscle mitochondria were incubated at varying clamped [ADP], we again observed the biphasic response to [ADP], but also found that the decrease in respiration was strongly associated with OAA accumulation. In addition, when a low (0.5 mM) concentration of pyruvate was added to metabolize OAA to citrate, the loss of succinate-supported respiration was reversed. Pyruvate (0.5 mM), added alone (without succinate), was essentially unable to support respiration. The effect of pyruvate to clear OAA and rescue succinate-supported respiration was blocked by inhibition of pyruvate uptake. Further, OAA accumulation with increasing [ADP] corresponded to a decrease in NADH consistent with utilization electrons by the transport system as malate was converted to OAA and consistent with OAA inhibition of SDH. We also found that the dynamic relationship of [ADP] to succinate-energized respiration varies according to muscle fiber type and specific body tissues in addition (as we reported in the past) to being affected in a rodent model of type 2 diabetes.

In summary, the biphasic respiratory response to succinate as respiration progresses from state 4 to 3 is initially triggered by [ADP]-dependent effects on membrane potential followed by inhibition of SDH by OAA.

Supported By: U.S. Department of Veterans Affairs

Prdx6 Prevents Diabetic Myopathy by Improving Skeletal Muscle Cell Differentiation
FRANCESCA PACIFICI, BARBARA CAPOIANI, FRANCESCA PIERMARINI, DONATELLA PASTORE, ROBERTO ARRIGA, ANDREA COPPOLA, SILVIA REA, GIULIA DONADEL, ALFONSO BELLOIA, DAVID DELLE-MORTE, DAVIDE LAURIDROME, Rome, Italy
Diabetes mellitus is characterized by a state of hyperglycemia resulting from altered insulin secretion by pancreatic beta cell, insulin action or both. This pathological condition is frequently associated with muscle mass loss, a condition defined as sarcopenia, and diabetic myopathy, represented by an impairment of the regenerative power of muscle fiber and by an altered differentiation of progenitor cells. Oxidative stress has been identified as the main cause of muscular alterations typical of diabetic patients. We showed that Peroxiredoxin 6 (Prdx6), a relatively new antioxidant enzyme belonging from the Peroxiredoxin family, has a central role in glucose homeostasis by exerting a potent antioxidant role. Based on these results, in the present study we aimed to verify whether Prdx6 modulates the association between diabetes and the progression of myopathy and sarcopenia. Firstly, we evaluated the gene expression of the main factors involved in the differentiation of myogenic muscle cells such as MyoD and Myogenin in murine knockout models for Prdx6 (Prdx6-/-). We observed significant decreased levels of both genes in Prdx6-/- mice compared to controls, suggesting an impairment of the regenerative potential of muscle fibers. These data were, also, confirmed by using in vitro cell model of murine myoblasts (C2C12) knockdown for Prdx6. Moreover, in the murine models, the process of muscle atrophy was studied by evaluating the gene expression of MuRF1 and Atrogin-1 that finely regulate protein degradation at skeletal muscle level. According to our hypothesis, the expression levels of both enzymes were significantly increased confirming the presence of muscle atrophy. Our study, for the first time, highlights a fundamental role of Prdx6 in the preservation of muscle mass, suggesting how Prdx6 can be considered a potential therapeutic target for diabetic myopathy and sarcopenia. However, further studies are needed in order to understand the molecular mechanism underlying this phenomenon.

Supported By: ADA-Supported Research

Mitophagy Receptor FUNDC1 Links Mitochondrial Quality Control to Muscle-Adipose Dialogue in Allleviating Dietary Obesity
TINGTING FU, ZHISHENG XU, LIN LIU, XIJUN LIANG, DANNIA ZHOU, QIQI GUO, LIWEI XIAO, ZHENJI GAN, Nanjing, China
The quality of mitochondria in skeletal muscle is essential for maintaining metabolic homeostasis during adaptive stress responses. However, the precise control mechanism of muscle mitochondrial quality and its physiological impacts remain unclear. Here, using two independent skeletal muscle-specific knockout mouse lines, we demonstrate that FUNDC1, a mediator of mitophagy, plays an essential role in controlling muscle mitochondrial quality as well as metabolic homeostasis. Mice with FUNDC1 deficiency in skeletal muscle (FUNDC1 mKO) showed decreased muscle fat utilization and endurance capacity (~40%) compared to WT littermates during exercise. Analysis of biochemical markers of mitophagy revealed a marked decrease in mitochondrial localization of LC3-II and PR6 protein levels, and this caused impaired mitochondrial respiration capacity. FUNDC1 loss-of-function studies in primary skeletal myocyte recapitulated defective mitophagy and impaired mitochondrial energetic as observed in FUNDC1 mKO muscle. Surprisingly, mice lacking muscle FUNDC1 were resistant to high fat diet (HFD) induced obesity despite reduced muscle mitochondrial energetics. Moreover, glucose and insulin tolerance tests demonstrated that HFD-fed FUNDC1 mKO mice were more tolerant to glucose challenge and more sensitive to insulin stimulation compared to HFD-fed WT controls. This seemingly paradoxical phenotype was due to enhanced fat burning in adipose tissue. HFD-fed FUNDC1 mKO mice had markedly elevated expression of key thermogenic genes such as Ucp1 (17-fold), Cidea (13-fold), and Dio2 (9-fold) in white adipose. Mechanistically, FUNDC1 deficiency elicited a retrograde response in muscle that upregulated FGF21 expression, thereby promoting the thermogenic remodeling of adipose tissue. Thus, these findings reveal a pivotal role of FUNDC1-dependent mitochondrial quality-control in mediating the muscle-adipose dialogue to regulate systemic metabolism.

Supported By: National Institutes of Health; Indian Council of Medical Research/National Institute for Research in Reproductive Health

Serum Creatinine Progressively Decreases with Obesity and Type 2 Diabetes in Nonhuman Primates
UDHAHAV K. CHAUDHARI, JENNIFER D. NEWCOMB, BARBARA C. HANSEN, Mumbai, India, Tampa, FL
Low muscle mass has been associated with insulin resistance and the development of type 2 diabetes (T2DM). Serum creatinine is a metabolite of creatine present in the skeletal muscle. The creatinine concentration is stable and directly proportional to skeletal muscle mass. Low levels of creatinine have been shown to be associated with the development of T2DM. The underlying mechanism of low creatinine and its risk for the development of diabetes is not known. Nonhuman primates (NHPs), maintained on a healthy diet, frequently develop spontaneous middle-aged obesity, metabolic syndrome (MetSyn), and T2DM similar to humans. In the present study, longitudinal evaluation of the associations between creatinine and the development of obesity, MetSyn, and T2DM in 125 male rhesus monkeys were studied. In addition, 7 male monkeys with long term calorie-restriction (CR) to maintain a healthy lean mass were used as a comparison group. Creatinine decreased as age (r=-0.39, p<0.001), body fat percent (r=-0.27, p<0.001), HbA1c% (r=-32, p<0.001) increased. Decrease in insulin sensitivity was significantly (r=-0.07, p<0.001) associated with a decrease in percent fat free mass. Creatinine also declined with decreasing insulin sensitiv- ity (r=0.23, p<0.05) and fat free mass (FFM) (r=-0.26, p<0.01) indicating that monkeys with higher lean muscle mass exhibited better insulin sensitivity. Creatinine was significantly decreased in monkeys with T2DM compared to both MetSyn and metabolically normal monkeys (p<0.001). Longitudinal data analysis showed progressive decline of creatinine with MetSyn and the development of T2DM. CR monkeys showed no significant change in creatinine throughout the lifelong duration of calorie restriction. Also unchanged during CR were fasting plasma glucose, body fat, FFM, or body weight. This is the first longitudinal study showing the association of creatinine with the development of T2DM. Serum creatinine levels declined with decrease in fat free mass and insulin sensitivity.

Supported By: National Institutes of Health; Indian Council of Medical Research/National Institute for Research in Reproductive Health

Thermogenic response to a cold challenge is partly regulated by uncoupling protein 1 (UCP1). In addition, UCP1 helps to dissipate excess energy into heat and prevent the development of obesity, MetSyn, and T2DM similar to humans. In the present study, we evaluated the expression levels of Ucp1 and other thermogenic genes such as Ucp2 (13-fold), Ucp3 (14-fold), Cidea (13-fold), and Dio2 (9-fold) in white adipose tissue. HFD-fed FUNDC1 mKO mice showed markedly elevated expression of key thermogenic genes such as Ucp1 (17-fold), Cidea (13-fold), and Dio2 (9-fold) in white adipose. Mechanistically, FUNDC1 deficiency elicited a retrograde response in muscle that upregulated FGF21 expression, thereby promoting thermogenic remodeling of adipose tissue. Thus, these findings reveal a pivotal role of FUNDC1-dependent mitochondrial quality-control in mediating the muscle-adipose dialogue to regulate systemic metabolism.
Insulin Resistance observed for malate (r² = 0.453, P < 0.01) and fumarate (r² = 0.501, P < 0.01) strengthened during insulin stimulation, with the strongest relationships that reflected a blunted increase in TCA intermediates during insulin stimulation.

Amino acids, including leucine, isoleucine and lysine, were negatively related to insulin sensitivity in the basal and insulin stimulated state (all P < 0.01). Together these findings indicated that physiologic insulin stimulation exacerbates metabolic signatures of skeletal muscle insulin resistance in humans.

Metabolomic profiling has identified signatures of insulin resistance in skeletal muscle; however, the direct effect of insulin stimulation on these metabolite signatures in humans remains largely unresolved. To address this, we investigated the effect of insulin stimulation on skeletal muscle metabolites in a well characterized cohort of humans spanning the spectrum of insulin sensitivity. Vastus lateralis muscle samples were obtained from endurance athletes, sedentary lean and obese adults, and individuals with type 2 diabetes (n=16,15,15,12, respectively) under basal conditions and 1-hour into a hyperinsulinemic-euglycemic clamp. Metabolic analysis was performed using UPLC-MS/MS. Basal concentrations of TCA cycle intermediates, including citrate, alpha-ketoglutarate, succinate, fumarate, malate and oxaloacetate, were positively related to insulin sensitivity (steady-state clamp R², glucose in mg/kg/min; all P < 0.01). Most of these relationships strengthened during insulin stimulation, with the strongest relationships observed for malate (R² = 0.453, P < 0.01) and fumarate (R² = 0.501, P < 0.01) that reflected a blunted increase in TCA intermediates during insulin stimulation with insulin resistance. Insulin stimulation lowered most medium- and long-chain acyl-carnitines compared with basal levels; however, this effect was also attenuated as a function of insulin resistance, signaling impaired metabolic flexibility. Notably, basal levels of several acyl-carnitines, including C12:0, C14:0, C16:0 and C18:1, were increased in endurance athletes compared with other groups (all P < 0.05). Several amino acids, including leucine, isoleucine and lysine, were negatively related to insulin sensitivity in the basal and insulin stimulated state (all P < 0.01).

Supported By: National Institutes of Health; National Institute of Diabetes and Digestive and Kidney Diseases (DK103829)
Skeletal Muscle Mitochondrial Fission Is Increased after an Overnight Lipid Influx in Healthy Humans

CIARAN E. FEALY, CHRISTOPHER L. AXELROD, MELISSA L. ERIKSON, EMMY HUANG, ADITHYA HARI, AMY MUIY, HISHASHI FUJIOKA, CHARLES L. HOPPEL, JOHN P. KIRWAN, HUANG, ADITHYA HARI, ANNY MULYA, HISASHI FUJIOKA, CHARLES L. HOPPEL, ORLANDO S. BROWN, ANDREW B. RYAN, and JOHN P. KIRWAN

TOPICAL UTILITY: Weight loss and exercise are known to improve insulin sensitivity. However, little is known about the cellular mechanisms behind this improvement. This study aimed to investigate whether increased mitochondrial fission (MF) could contribute to improved insulin sensitivity (IS). We studied forty subjects who competed a randomized controlled trial (RCT) consisting of 6 months of either Health Education Control (CON: n=13 SM/8F), Diet-induced weight-loss only (DIWL: n=13 SM/8F), or Weight-loss and Exercise (WLEX: n=14 SM/9F). 

METHODS: 

METHODS: We compared MF, mitochondrial respiration, and mitochondrial membrane potential (TMRM staining) by confocal microscopy, oxidative protein expression were assessed by western blot, ex vivo mitochondrial respiration, and circulating circulating lipid species by mass spectrometry. The DIWL and WLEX groups both lost a significant amount of weight compared to CON (DIWL: -6.4%, WLEX: -11.3%, CON: -2.5%, P<0.05). IS measured as the glucose infusion rate required to maintain euglycemia during the clamp increased in the DIWL and WLEX groups compared to the control group (DIWL: 1.0, WLEX: 2.7, CON: 0.6 mg/kg/min, P<0.05). Total phosphatidylethanolamine (PE), phosphatidylcholine (PC), dacylglycerols (DAG) did not significantly change in IS. We studied forty subjects who competed a randomized controlled trial (RCT) consisting of 6 months of either Health Education Control (CON: n=13 SM/8F), Diet-induced weight-loss only (DIWL: n=13 SM/8F), or Weight-loss and Exercise (WLEX: n=14 SM/9F). DIWL and WLEX subjects had a goal of 10% weight-loss through calorie restriction. Hyperinsulinemic-euglycemic clamp was employed to measure IS, and muscle biopsies were obtained to quantify intramyocellular lipids by mass spectrometry. The DIWL and WLEX groups both lost a significant amount of weight compared to CON (DIWL: -6.4%, WLEX: -11.3%, CON: -2.5%, P<0.05). IS measured as the glucose infusion rate required to maintain euglycemia during the clamp increased in the DIWL and WLEX groups compared to the control group (DIWL: 1.0, WLEX: 2.7, CON: 0.6 mg/kg/min, P<0.05). Total phosphatidylethanolamine (PE), phosphatidylcholine (PC), dacylglycerols (DAG) did not significantly change following intervention (P>0.05). However, there were trends for unsaturated PE and PC species to increase in the WLEX only and saturated DAG and ceramide species to be reduced in both the DIWL and WLEX group. The increase in unsaturation of PE and PC were associated with improvements in IS (PE: P=0.047, r=0.35; PC: P=0.072, r=0.32) and the decrease in saturation of DAG was associated with improvements in IS (P=0.044, n=0.36).

In conclusion, weight-loss and exercise increase unsaturated PE and PC species, and reduce saturated DAG species, which are related to improved IS within skeletal muscle. 

Supported By: National Institutes of Health (RTA0202161 to B.H.)

Circulating Pigment Epithelium-Derived-Factor Levels—Hyperglycemia vs. Insulin Resistance

RAELENE E. MASER, JAMES LENHARD, RYAN FOHLIS, P. BABU BALAGOPAL, NEWARK, DE; WILMINGTON, DE; JACKSONVILLE, FL

TOPICAL UTILITY: Although studies have suggested PEPF’s role in mediating insulin resistance, its potential role with regard to glycemic control remains unclear. We examined the association of serum PEPF and glycemic control in individuals with T2D (n=50; 21 men/29 women; age=63±10 years; CKD-stage 3b). PEPF was higher for those in poor (HbA1c≥7%: n=26) glycemic control (12.6±3.3 vs. 11.2±2.2 μg/mL, P=0.047) and for those that were insulin resistant (HOMA-IR≥1.8: n=23, P<0.05). Spearman rank correlations of PEPF included: HbA1c≥7% (r=0.27, p=0.059), HOMA-IR≥1.8 (r=0.30, p=0.037), triglycerides (r=0.53, p<0.001), creatinine (r=0.51, p<0.001), and AST (r=0.33, p=0.02). Linear regression, with PEPF as the dependent variable, revealed that AST (p=0.003), creatinine (p=0.001), and poor glycemic control (HbA1c≥7%) (p=0.009) were significant correlates (model R²=0.63, p<0.001) whereas insulin resistance (HOMA-IR≥1.8) was not (p=0.70). There was also a significant interaction of AST x creatinine (p=0.02). While some suggest that elevated PEPF levels are associated with insulin resistance, the lack of an association in our data is intriguing. It is possible that glycopenegosis by the liver and kidney is associated with elevation in circulating PEPF and PEPF may be part of an incomplete self-defense regulatory mechanism to limit hyperglycemia. The significant interaction suggests that the relationship between creatinine and PEPF depends on AST. Taken together, the association between PEPF and poor glycemic control in persons with T2D may suggest a preferentially protective compensatory response of PEPF against hyperglycemia but not insulin resistance.

Supported By: Innovation Fund Denmark; Vissing Foundation
Assessment of Fasting Glucagon Levels in Subjects with Diabetes and Healthy Controls Using ELISA and RIA

MARTINA BRUNNER, MAXIMILIAN HABERLANDER, EVA SVEHLIKOVA, KATHARINA EBERHARD, ELISABETH STACH, THOMAS R. PIEBER, HARALD SOURIJ, AUSTRIAN DIABETES SOCIETY (ADA)-SUPPORTED RESEARCH

1941-P

Objective: To determine the fasting glucagon levels in subjects with diabetes and healthy controls using two different standard immunoassays (Elisa and Ria).

Methods: 20 T1D patients, 20 T2D patients, and 20 healthy controls participated in the study. Fasting glucagon levels were measured using an idiom immunoassay (ELISA) and an RIA technique.

Results: The median glucagon levels were significantly higher in T1D patients (3.6 ng/mL) compared to healthy controls (2.1 ng/mL) and T2D patients (2.9 ng/mL). A similar trend was observed for RIA measurements.

Conclusion: Fasting glucagon levels are elevated in subjects with type 1 diabetes compared to healthy controls and type 2 diabetes. These findings may have implications for the understanding of pancreatic alpha-cell function in diabetes.

Supported By: Novo Nordisk Pharma Ltd., Japan Diabetes Society
Risk of Breast Cancer According to Glycaemia and HbA1c Concentration—A Meta-analysis of Prospective Studies

Alina Macace, Cecile Pizot, Peter Boyle, Philippe Autier, Eculy, France, Lyon, France

Some observational studies have suggested that women with diabetes may be at an increased risk of breast cancer. Blood levels of fasting glucose (FG) and of glycated hemoglobin (HbA1c) are major diagnostic tools for diabetes. The aim of this study was to investigate the association between HbA1c, FG and breast cancer occurrence. A systematic literature search identified prospective studies which reported a quantitative estimate of the association between HbA1c or FG and breast cancer. Summary relative risks (SRR) of breast cancer, comparing high vs. low levels of HbA1c or FG, were computed using random-effect meta-analysis. Ten studies for HbA1c (116,035 women and 3,095 breast cancer cases) and 13 studies for FG (571,071 women and 14,579 breast cancer cases) were selected. High levels of HbA1c (FG) ranged from >4.5% to ≥9% (>5 to >7.8 mmol/L), and low level ranged from <3.3% to <7.1% (<4 to <6.1 mmol/L). Overall, the SRR of breast cancer was 0.97 (95% CI: 0.76, 1.24) for HbA1c and 1.15 (95% CI: 1.01, 1.33) for FG, with moderate heterogeneity between studies (I²=44% and 45%, respectively). When the analyses were restricted to women with HbA1c >6.5% and FG >7mmol/L, the SRR was 0.97 (95% CI: 0.81, 1.15) for HbA1c (six studies) and 1.15 (95% CI: 1.01, 1.31) for FG (seven studies) without heterogeneity in both analyses (I²=0%). In 3 studies conducted in diabetic women, the SRR for the association between HbA1c levels and breast cancer was 0.95 (95% CI: 0.79, 1.15) with no heterogeneity (I²=0%). No study was found on FG among diabetic women only. No association was found between HbA1c and breast cancer occurrence, while fasting glucose might be associated with a slight increased risk. The lack of clear association suggests that the increased risk of breast cancer observed among diabetic women appears to be driven by factors other than the blood glucose concentration disorders.

Endo Soc-3-Decrease in AMP Kinase Expression and Activity in Diabetic Patients with Hypogonadism—Increase Following Testosterone Supplementation

Sanjay Chhoda, Husam Ghanim, Manav Batra, Ajay Chaudhuri, Sanada Abujayshah, Fares Dandoon, St. Louis, MO, Buffalo, NY, Williamsburg, NY

AMP kinase is a key enzyme involved with energy regulation, the intake of macronutrients, the uptake of glucose and fatty acids by cells and the metabolic combustion of fatty acids. We hypothesized that in patients with hypogonadism associated with diabetes, its expression and activity are diminished since there is a quantitative and qualitative loss of skeletal muscle function. Twenty-two men with HH and T2DM were compared with 20 eugonadal men with T2DM at baseline. From the HH patients, 12 were treated with testosterone 200 mg every 2 weeks injected intramuscularly for 24 weeks, during which their plasma concentrations were maintained in the physiological range. Hyperinsulinemic, euglycemic clamps (HEC) were carried out prior to and after HEC procedure on each occasion. In the hypogonadal state, the expression and the activity (measured as phoso-T172-AMPK-α) of AMP kinase-α was significantly lower in HH patients than eugonadal diabetics both in adipose tissue and skeletal muscle by 37% and 29%, respectively, for expression and by 22% and 28%, respectively, for activity. Following testosterone, there was no change in expression but there was a significant increase in AMP kinase activity by 69.31% (from 14.9±2.8 to 22.8±2.2 U/mL, p<0.05) in the muscle but not in the adipose tissue. At the end of the treatment and following the hyperinsulinemic euglycemic clamp, there was a significant increase in AMP kinase expression by 41.9% and 46.1% in adipose tissue and muscle, respectively, for expression and by 22% and 28%, respectively, for activity. Following testosterone, the increased AMP kinase expression and activity in both tissues. Clearly, therefore, testosterone is an important modulator of AMP kinase activity. This effect of testosterone may contribute to the increase in glucose uptake and an improvement in insulin sensitivity since AMPK kinase also induces an increase in Akt2 and GLUT-4 expression.

Hepatic Insulin Clearance Is Increased in the Patients with Poorly Controlled Type 2 Diabetes

Tsuyoshi Okura, Mari Anno, Yuichi Ito, SR, Yonago, Japan

Aim: The hepatic insulin clearance (HIC) is an important pathophysiology of type 2 diabetes mellitus (T2DM). Some studies reported that HIC was decreased in the patients with T2DM. However, a basic research reported that hyperglycemia enhances HIC, and it is not well-known whether poorly controlled diabetes increases HIC in the patients with T2DM. We investigated whether HIC was increased in the patients with poorly controlled diabetes, and we also evaluated whether HIC associated with insulin resistance.

Methods: We performed meal tolerance test and hyperinsulinemic-euglycemic clamp for 23 patients with type 2 diabetes (mean HbA1c 7.5%). We calculated the postprandial C-peptide/AICU/LIC ratio as HIC.

Result: The HIC significantly correlated with HbA1c (R=0.60, P<0.005). In the patients with high HIC above the median, the mean HbA1c was significantly higher than that of low HIC below the median (7.95% vs. 6.89%, P<0.01). The HIC was not correlated with insulin resistance as evaluated by the glucose clamp method (R=0.29, P=0.16).

Conclusion: These results suggested that hepatic insulin clearance was increased in the patients with poorly controlled T2DM, especially in the patients with HbA1c≥8%.

Supported By: Japan Society for the Promotion of Science

Metabolomics Shows an Association of Betatrophin with Bile Acids, Suggesting an Involvement of Betatrophin in Bile Acid-Meditated Metabolic Control

Andreas Lehnerer, Axel Muendlein, Kathrin Geiger, Christoph H. Saely, Eva-Maria Brandtner, Janine Ebner, Barbara Larcher, Arthur Mader, Peter Fraunberger, Heinz Drexel, Triesen, Liechtenstein, Feldkirch, Austria, Bern, Switzerland, Philadelphia, PA

Betatrophin, also known as ANGPTL8, is secreted by liver and adipose tissue and plays an important role in glucose and lipid metabolism, but the mechanisms behind this remain unclear. Betatrophin is highly activated by active triiodothyronine (T3), a key player in metabolic control, which in turn is activated by bile acids (BA) via the BA-6-protein-coupled receptor TGR5-cAMP-αMK-deiodinase (D2), mediating the conversion of prohormone thyroxine to T3. We here measured betatrophin by ELISA and also applied GWAS and targeted metabolomic profiling in 232 serum samples of coronary angiographed patients. We found a correlation between betatrophin and BMI (r=0.142, p<0.001), fasting glucose (r=0.133, p=0.002), insulin (r=0.221, p<0.001), triglycerides (r=0.233, p<0.001), HDL (r=-0.122, p=0.004), and albumin (r=0.247, p<0.001). GWAS also found a genome-wide association between betatrophin and genomic variants in sterol transporter genes ABCG5/G8 and ABCA1. In the metabolic assays we identified BA as the top metabolite to be associated with betatrophin concentration in serum (CDCA, r=0.234, p<0.001; GCA, r=0.247, p<0.001; GCDCA, r=0.268, p=0.004; oxLDL (r=0.247, p<0.001).

In conclusion, this study for the first time describes the association between betatrophin and BA. As (i) T3 is activated by BA via the BA-TGR5-CAMP-D2 signalling pathway and (ii) T3 is a strong activator of betatrophin, the link between betatrophin concentration and BA suggests that, at least in part, the impact of BA on energy homeostasis and metabolic control may be mediated via betatrophin. Moreover, TGR5 receptors have also been identified on pancreatic β-cells and β-cells and are stimulating insulin secretion in β-cells and able to restore β-cell mass and function under hyperglycemic conditions. Altogether, this may elucidate the impact of betatrophin on lipid and glucose metabolism.

Lactobacillus Gasseri in the Upper Small Intestine Impacts an ACSL3-Dependent Fatty Acid Sensing Pathway That Regulates Whole-Body Glucose Homeostasis

Paige V. Bauer, Frank Duca, T.M. Zaved Waise, Helen J. Dranse, Britany A. Rasmussen-small, Akshtia Purii, Mohgan Rasti, Tony K.T. Lam, Toronto, ON, Canada, Tucson, AZ

Long chain acyl CoA synthetase (ACSL)-dependent upper small intestinal lipid metabolism activates preabsorptive pathways to regulate metabolic homeostasis, but whether changes in the upper small intestinal microbiota after specific fatty acid-dependent pathways to impact glucose homeostasis remains unknown. We here first find that upper small intestinal infusion of trioleic, oleic acid, or linoleic acid preabsorptively increases glucose tolerance and lowers glucose production in rodents. High-fat feeding impairs preabsorptive fatty acid sensing and reduces upper small intestinal Lactobacillus gasseri levels and ACSL3 expression. Transplantation of healthy upper small intestinal microbiota to high-fat fed rodents restores Lactobacillus gasseri levels and fatty acid sensing via increased ACSL3 expression, while Lactobacillus gasseri probiotic administration to non-transplanted high-fat fed rodents is sufficient to restore upper small intestinal ACSL3 expression and fatty acid sensing.

In summary, we unveil a glucoregulatory role of upper small intestinal Lactobacillus gasseri that impacts an ACSL3-dependent glucoregulatory fatty acid sensing pathway.

Supported By: Canadian Institutes of Health Research
of the rarity of CS, there are few studies that assessed whether glucose dysfunction caused by cortisol overproduction is reversible. 

\[ \beta \text{-cell function were largely ameliorated after surgery for CPA, indicating that} \]

significant (0.70 [0.22-1.51] to 1.22 [0.78-1.64], \( p = 0.04 \), and 609.1 [237.8-1095.2] to 990.0 [598.6-1668.6], \( p < 0.001 \)). In addition, the insulinogenic and disposition indices increased significantly (2.4 [1.4-2.8] to 1.0 [0.6-1.1], \( p = 0.002 \)), and the Matsuda index increased significantly (3.3 [2.3-4.5] to 6.2 [6.3-11.4], \( p < 0.001 \)). In addition, the insulogenic and disposition indices increased significantly (0.70 [0.22-1.51] to 1.22 [0.78-1.64], \( p = 0.04 \), and 609.1 [237.8-1095.2] to 990.0 [598.6-1668.6], \( p = 0.001 \)). In conclusion, our study indicated that insulin resistance and insulin secretion were largely ameliorated after surgery for CPA, indicating that \( \beta \text{-cell dysfunction caused by cortisol overproduction is reversible.} \]

Roles of Adipose Tissue VLDL-VLDLR Axis in Energy Metabolism

JAE BUM KIM, KYUNG CHEUL SHIN, INJAE HWANG, SUNG SIK CHOE, Seoul, Republic of Korea

Elevated plasma triglyceride-rich lipoprotein, such as very low-density lipoprotein (VLDL), is considered a risk factor for prevalence of obesity, type 2 diabetes mellitus, and atherosclerosis. VLDL receptor (VLDLR), one of the lipoprotein receptor family proteins, is involved in clearance of circul-
INTEGRATED PHYSIOLOGY—OTHER HORMONES

1954-P

Exenatide and Saxagliptin Do Not Attenuate NFXB-Induced Inflammation in Prediabetic Humans

ABASLON D. GUTIERREZ JR., KARLA BERMEJUE, VALA HAMIDI, KAYLA RIGGS, SARA COVERDALE, AMY DURSTELDER, NATIA K. KUMAR, MONIKA RUSCHENSKY, HOUSTON, TX; SAN DIEGO, CA; DALLAS, TX

Incretin mimetic medications acutely downregulate inflammation via the NFκB pathway during the fasting state in humans with type 2 diabetes mellitus. Free fatty acids (FFAs) activate TRAIL, stimulating NFXB and the production of IL-6, which downregulates insulin signaling via SOCS3. We investigated this pathway in the acute postprandial state—utilizing a high-fat meal and incretin mimetic therapies—in humans with prediabetes. Sixteen humans with prediabetes (age 50 ± 2 years, BMI 32.5 ± 0.4 kg/m², HbA1c 5.96 ± 0.05%) participated in a randomized, double-blinded trial comparing exenatide, saxagliptin, and placebo. Blood was drawn at baseline (fasting) and 2 hours for the collection of peripheral blood mononuclear cells (PBMCs) and plasma. After baseline blood draw, subjects were given study medication followed by high-fat test meal. Procedures were repeated for all study arms. Subsequently, seven of these subjects (age 51 ± 2 years, BMI 33.3 ± 0.6 kg/m², HbA1c 5.96 ± 0.17%) participated in an open-label extension study after the administration of exenatide extended-release (EXR) for six weeks. The above procedures were repeated. In the randomized trial, plasma FFA decreased in all groups (p<0.05), though the magnitude of decrease was smaller for exenatide. Plasma IL-6 levels increased in all groups except the saxagliptin (p<0.05). Western blots of PBMCs showed no significant changes in levels of NFXB, TRAIL, or SOCS3. Plasma insulin did not change in the exenatide group but increased in other groups. In the extension study with EXR, plasma FFA decreased between 0 and 2 hours (p<0.05), and to a greater extent than the prior exenatide group. Plasma IL-6 levels decreased (p<0.05) and insulin levels increased (p<0.05). Western blots showed no significant changes in levels of NFXB, TRAIL, or SOCS3. These data show that six weeks of EXR significantly reduced postprandial FFA levels and IL-6 without any noted changes in NFXB pathway between 0 and 2 hours.

Supported By: National Institutes of Health (UL1TR000371); National Center for Advancing Translational Sciences (K27TR000370)

1955-P

SGLT1 in Pancreatic α Cells Regulates Glucagon Secretion in Mice, Possibly Explaining the Distinct Effects of SGLT2 Inhibitors on Plasma Glucagon Levels

TAKAYOSHI SUGA, OSAMU KIKUCHI, MASAKI KOBAYASHI, SHO MATSUI, HIROMI H. HASHIMOTO, TSUTOMU SASAKI, SATORU KAKAZKI, MASANOBU YAMADA, TADAHIRO KITAMURA, MBAEBASHI, Japan

A recent report described that sodium glucose cotransporter (SGLT) 1 and 2 were expressed in α cells, and dapagliflozin which is a specific SGLT2 inhibitor, increased plasma glucagon levels in isolated α cells. However, it is still controversial whether SGLT1 inhibitors increase plasma glucagon levels in vivo. Here, we showed that dapagliflozin, but not canagliflozin which is a SGLT2 low-potency-SGLT1 inhibitor, increased plasma glucagon levels in mice fed a high-fat, high-sucrose diet (HFHS) and diabetic db/db mice. A glucose clamp study revealed that the plasma glucagon increase associated with dapagliflozin could be explained as a response to acute declines in blood glucose. RT-PCR and whole RNA sequencing revealed that SGLT1 and glucose transporter 1 (GLUT1), but not SGLT2, were expressed in α cells and mouse islets. We showed that canagliflozin suppressed glucagon secretion by inhibiting SGLT1 in α cells; consequently, plasma glucagon did not increase with canagliflozin, even though blood glucose decline. We also showed that the SGLT1 effect on glucagon secretion depended on sodium/glucose cotransport, but not on metabolic effect of glucose. Islets from HFHS and db/db mice displayed higher SGLT1 expression and lower GLUT1 expression than the islets from control mice. These expression levels were associated with glucagon secretion levels.

SGLT1 inhibitor and siRNA against SGLT1 suppressed glucagon secretion in isolated islets. These data suggested that a novel mechanism regulated glucagon secretion, through SGLT1, in α cells. This finding explained the distinct effects of dapagliflozin and canagliflozin on plasma glucagon levels in mice.

Supported By: Mitsubishi Tanabe Pharma Corporation; AstraZeneca K.K.

1956-P

Effects of Simple Carbohydrates on GLP-1 Responses in Gastric Bypass Patients and Matched Controls

CHRISTOFFER MARTINSSON, KIRSTINE N. BOJSEN-MOLLER, CARSTEN DIRKSEN, MARIA S. SVANE, JENS J. HOLST, STEN MADSBAD, SR., COPENHAGEN, Denmark; HUDVÆRE, Denmark

Exaggerated postprandial secretion of GLP-1 seems to contribute importantly to the metabolic effects of Roux-en-Y gastric bypass (RYGB). The surgery accelerates nutrient entry to the distal intestine, which is believed to augment GLP-1 secretion. In un-operated individuals, slowly digested carbohydrates are also absorbed in the distal intestine and may accordingly produce greater GLP-1 responses than rapidly absorbed ones.

Our aim was to investigate GLP-1 secretion in response to isomolar (0.1385 mol) oral loads of glucose (glu) and fructose (fru), either given as a separate monosaccharides (25 g glu and 25 g fru) or as disaccharides in the form of 47.5 g sucrose (suc) +/- alpha glucosidase inhibition (by acarbose (aca)) or 47.5 g isomaltulose (iso), which is slower digested than suc, on 4 separate days in 10 RYGB patients and 10 controls (CON) matched on BMI, age and sex.

Glu/fru and suc induced similar glucagon responses and responses of C-peptide and GLP-1, the latter being 3-fold greater in RYGB compared to CON. Digestion of iso was slow in comparison with suc in both groups. Mean GLP-1 response (positive iAUC) to iso was ~50% and ~180% greater than to suc in RYGB (p<0.01) and CON (p<0.01), respectively. Aca effectively slowed suc digestion in both groups, resulting in lower peak concentrations of glucagon (RYGB: 3.9 ± 6.7 mmol/l; CON: 7.7 ± 6.6 mmol/l) and C-peptide (RYGB: 2762 ± 1341 pmol/l; CON: 2367 ± 1520 pmol/l) with aca alone (p<0.01). Aca diminished mean suc stimulated GLP-1 secretion by ~50% in RYGB (p<0.01), but this effect was absent in CON.

The slowly absorbed disaccharide isomaltulose elicits a greater GLP-1 response than sucrose. The same effect is not evident when digestion of sucrose is inhibited by acarbose, which in RYGB diminishes sucrose induced GLP-1 secretion. Understanding the digestive processes involved in carbohydrate induced GLP-1 release after gastric bypass is an important step towards mimicking the effects of the surgery by pharmacological means.

Supported By: Novo Nordisk Foundation; Danish Diabetes Academy; Hudvære Hospital

1957-P

Exendin-4, a Glucagon-Like Peptide-1 Receptor Agonist, Attenuates Prostate Cancer Cell Proliferation via Phosphorylation of MKP-1

TAKAKI KAWANAMI, TAKASHI NOMIYAMA, YURIKO HAMAGUCHI, TOMOKO TANAKA, TOSHIHIKO YANASE, TAKAKO KAWANAMI, TAKASHI NOMIYAMA, YURIKO HAMAGUCHI, TOMOKO TANAKA, TOSHIHIKO YANASE, Fukui, Japan

Pleiotropic benefits of incretin therapy beyond glycemic control have been reported and receiving much attention. Cancer is one of major causes of death in patients with type 2 diabetes. We have previously reported Exen-4 (Ex-4), a glucagon-like peptide-1 receptor agonist, attenuates prostate cancer growth by the inhibition of ERK/MAPK phosphorylation (Diabetes 2014). On the other hand, it is well known that MAPK is inactivated and tightly regulated by MAPK phosphatase (MKP) family. Then, we next examined whether MKP could be involved in the anti-proliferative effect of Ex-4 in the prostate cancer cell. In a human prostate cancer cell line, LNCaP cell, MKP-1 was abundantly expressed. Knocking down of MKP-1 using siRNA abolished Ex-4-induced reduction of LNCaP cell number in growth curve. In addition, Ex-4 treatment significantly increased MKP-1 mRNA expression. To activate its phosphatase activity, Ser369 in the C terminus of MKP-1 is specifically phosphorylated. Ex-4 significantly phosphorylated Ser369 of MKP-1 faling with time course of dephosphorylating ERK/MAPK. Using immunoprecipitation assay, we further confirmed that Ex-4 exactly phosphorylated Ser369 of MKP-1. In addition, if we transiently transfected GFP conjugated MKP-1 into LNCaP cells, nuclear translocation of MKP-1 induced by Ex-4 treatment was observed in early phase stimulation. These data suggest that Ex-4 attenuates prostate cancer cell proliferation via phosphorylation of MKP-1 followed by inhibition of ERK/MAPK activation.

Supported By: Mitsubishi Tanabe Pharma Corporation; AstraZeneca K.K.
Incretin hormone release does not involve hepatic portal vein glucose sensors.

DALE S. EGERDING, GUILLAUME KRAFT, MARIA S. SMITH, L. MERKLEY MOORE, BERN FARMER, HEATHER SARA, MELANIE SCOTT, MARY MOORE, MICHAEL A. NAUCK, ALAN D. CHERINGTON, NASREDDIN OSMAN, ARTHUR CHANG, ANDREW A. YOUNG, MELANIE SCOTT, ANDREW A. YOUNG, DONG WANG, WENJUN CHEN, ANDREW A. YOUNG, ANDREW A. YOUNG.

Background: The portal vascular system is a significant regulator of hepatic glucose balance and is of obvious importance in regulation of basal and postprandial glucose production. In addition,portal vein glucose (PVG) is an important substrate for portal-first glucose production.

Aim: To determine whether incretin hormones, Glucagon Like Peptide 1 (GLP-1) and Glucose dependent Insulinotropic Peptide (GIP), are released in response to glucose ingestion via the portal vein.

Methods: In vivo studies were performed on Sprague-Dawley rats using portal and central arterial catheters to collect arterial and portal vein blood samples. Rats were given either a low (10 mg/kg/min) or high (100 mg/kg/min) intraportal (IP) glucose infusion. Portal glucose levels were then measured and compared to central arterial glucose levels following the same IP glucose doses. Portal vein glucose levels were also measured in rats given exogenous PVG via the hepatic portal vein (HVP). Rats were given a glucose load (10 mg/kg/min via portal vein) and portal glucose levels were measured at various time points following IP injections of 0, 1 and 5 µg/kg/min GLP-1 and 0 and 5 µg/kg/min GIP.

Results: Portal glucose levels were significantly greater in the IP and HVP groups compared to controls (C). Portal glucose levels were also significantly elevated in response to exogenous PVG and IP injections following GLP-1 and GIP injections. No significant differences were found between portal and central arterial glucose levels in response to IP injection of GLP-1 and GIP in either group.

Conclusions: Portal vein glucose levels are elevated in response to IP injection of GLP-1 and GIP. Portal vein glucose levels are significantly elevated in response to exogenous portal vein glucose (HVP). Portal glucose levels are not increased in response to IP injection of GLP-1 and GIP in either group.
in both GcgRAΔ3AR and GcgRAΔ3ARΔβ3 mice was about 50% of control animals. LPS first increased, then significantly decreased blood glucose in control, pancreatic and intestinal reactivated mice but was significantly lower across all time points in Gαi null mice. These data suggest that both intestinal and pancreatic sources contribute to the increase in plasma GLP-1 seen in our model of sepsis. However, either pancreatic or intestinal sources of GLP-1 are sufficient to maintain glucose responses to LPS.

1963-P

Glucagon-Like Peptide-1 Is a Significant Determinant of the Second-Meal Effect in Patients with Type 2 Diabetes

SIGRID BERGMANN, NATASHA C. BERMANN, LEREKE S. GASJUERI, JENS J. HÖLST, TINA VILSBÆLL, FILIP K. KNØP, Hellerup, Denmark, Copenhagen, Denmark, Gentofte, Denmark

Background and Aims: The mechanisms behind the second-meal effect, i.e., the capability of a small premeal to reduce plasma glucose excursions during a main meal in type 2 diabetes, remain unknown. We investigated the involvement of the gut-derived hormone glucagon-like peptide-1 (GLP-1) in the second-meal effect in patients with type 2 diabetes.

Methods: In a randomized, double-blinded, placebo-controlled, double-dummy, cross-over study, the second-meal effect was investigated in 15 male patients with metformin-treated type 2 diabetes over two days by administering a premeal (30 g of whey protein in 100 ml water) or a non-caloric flavor-controlled drink 30 minutes before a standardized liquid main meal. During both conditions, the second-meal effect was evaluated twice: with concomitant infusion of the GLP-1 receptor antagonist exendin[9-39] and saline (placebo), respectively.

Results: A second-meal effect was observed in 9 out of 15 participants, defined as responders, in whom the premeal significantly reduced postprandial glucose excursions during the main meal by 11% (assessed by area under the plasma glucose curve). The second-meal effect was completely abolished by iv infusion of exendin[9-39], during which the premeal resulted in a 5% exacerbation of postprandial glucose excursions. Significant GLP-1-mediated second-meal effects on postprandial insulin (56%) and C-peptide responses (86%) were also observed.

Conclusions: By antagonizing the GLP-1 receptor, premeal-induced beta cell secretion is significantly reduced and the glucose-lowering effect of a premeal on a subsequent main meal, the second-meal effect, is annulled in patients with type 2 diabetes. This suggests that premeal-induced GLP-1 secretion constitutes a significant determinant of the second-meal effect in type 2 diabetes patients.

Supported By: Novo Nordisk Foundation

1964-P

The Role of Visceral Adipocytes in Adrenergically Stimulated Adiponectin Secretion

SALIJA MUŠOVIC, SANDRA NIGUYEN, CHARLOTTA S. OLOFSSON, Gothenburg, Sweden

Adiponectin is a white adipocyte hormone with insulin sensitizing properties. Correlations have been observed between adiponectin and different adipose tissue depots. Our model of beige adipocytes shows a negative relationship to visceral fat mass (VAT). Individuals with increased VAT have a greater risk for developing type 2 diabetes. We have previously shown that catecholamines stimulate acute adiponectin release from subcutaneous adipocytes via adrenergic beta-3 receptors (β3ARs) and Epac1. We further showed that this adrenergic stimulation was abolished in obesity/diabetes due to reduced levels of both β3ARs and Epac1. Here we aim to study the adrenergically stimulated adiponectin secretion in visceral adipocytes in health and in metabolic disease. Results obtained by ELISA revealed that epinephrine (EPI) and CL316243 (CL; β3AR agonist) stimulated adiponectin release to a similar degree (-2 fold) in primary visceral mouse adipocytes during 30 minutes incubation. The stimulatory effect of EPI was inhibited by Epac antagonist ESI-09 (P<0.05). Studies using visceral adipocytes isolated from obese/diabetic mice demonstrated that adiponectin release could still be stimulated with EPI and CL (-1.5 fold) although at a significantly lower magnitude compared to control mice (P<0.001). RT-qPCR results showed a high expression of βAR as well as Epac1 in adipocytes isolated from control mice. In adipocytes isolated from obese/diabetic mice there was no change in expression of βAR but an increase of Epac1 (P<0.001). Our results propose that acute adiponectin release in visceral adipocytes is regulated through activation of βAR and Epac1. It is an interesting finding that VAT adipocytes which are connected to several metabolically active organs largely maintain adrenergically stimulated adiponectin release in obesity/diabetes.

1965-P

Gastrin—A Potential Predictor of Glucoregulation in Newly Diagnosed Type 2 Diabetes Patients

MAJA CIGROVIĆ BERKOVIC, DAVORKA HERMAN MAHECIC, INES BILIC-CURIC, Zagreb, Croatia, Croatia

Background and Aims: Experimental data demonstrated that activation of GLP-1 and gastrin signaling induces beta cell neogenesis, resulting in a promotion of glucose-induced insulin secretion. In addition, treatment with proton pump inhibitors is associated with greater glycemic control in patients with type 2 diabetes (T2DM), particularly in those on insulin- or GLP-1-based therapy. The aim of this study was to assess gastrin as a potential predictor of beta cell function and glucoregulation in newly diagnosed T2DM patients.

Materials and Methods: In this cross sectional study 190 patients (64 males and 126 females) with new onset T2DM were included. Patients treated with IPGs were excluded. Fasting plasma glucose (FPG), postprandial PG, HbA1c, fasting insulin, pancreatic β-cell function (HOMA-B), insulin resistance index (HOMA-IR), fasting c-peptide and gastrin levels were measured at the time of diagnosis.

Results: Baseline HbA1c was 7.53±2.08%, average age of patients was 61.8±10.05 years and body mass index (BMI) was 31.25±5.73 kg/m². Parameters of glucoregulation were not significantly correlated with gastrin (all p>0.05), while there was moderate negative correlation with HOMA-B (HbA1c, FPG and PPG, p<0.01 for all) and positive correlation with HOMA-IR (HbA1c, FPG and PPG, p<0.01 for all). Patients with higher baseline measures of glucose regulation had lower HOMA-B and higher HOMA-IR as was expected. There was no association between gastrin and HOMA-B (p>0.05) or HOMA-IR. Furthermore, there was no association established between c-peptide, insulin levels and gastrin (p>0.05).

Conclusion: Baseline gastrin levels are not sufficient to have a significant effect on glucoregulation or HOMA-B and HOMA-IR in newly diagnosed T2DM, therefore it could be postulated that further stimulation of gastrin secretion (e.g., with IPGs or GLP-1 based therapy) is needed in order to influence beta cell function and glycemic control.

1966-P

miR-494 Regulates Mitochondrial Biogenesis and Thermogenesis through PGC1-α Signaling in Beige Adipocytes

MENGSTU LEMECHA, KATSUTARO MORINO, TAKESHI IMAMURA, HIROTAKE IWASAKI, NATSUOKO OHASHI, HIROTAKE YAMAMOTO, SATOSHI UGI, HIROSHI MAEDAWA, Osaka, Japan, Japan, Japan

Background: Mitochondria play an essential role in the heat generation in beige adipocytes. Their number and function are regulated in response to external stimuli such as cold exposure and beta-3 adrenergic receptor (β3-AR) agonist. Previously, we have reported that miR-494 regulates mitochondrial biogenesis in the skeletal muscle. However, this remains unknown in beige adipocytes.

Aim: We investigated the role of miR-494 on mitochondrial biogenesis during adipogenesis and browning.

Result: C57BL/6J mice were subjected to intermittent mild cold exposure. The expression levels of peroxisome proliferators activated receptor gamma coactivator 1-alpha (PGC1-α) and mitochondrial proteins including mitochondrial transcription factor A (TFAM), pyruvate dehydrogenase (PDH), mitochondrial encoded cytochrome c oxidase (MTCO1) and uncoupling protein 1 (Ucp1) were strongly increased in inguinal white adipose tissue (IWAT). On the contrary, that of miR-494 resulted in 27% reduction (p<0.05) in IWAT following 12°C cold exposure for 6 hours. Furthermore, β3-AR stimulation potently reduced miR-494 expression in 3T3-L1 beige cells. Overexpression of miR-494 substantially reduced the protein expression of PGC1-α and its downstream targets such as TFAM and MTCO1 and uncoupling protein 1 (Ucp1) were strongly increased in inguinal white adipose tissue (IWAT). On the contrary, the expression of miR-494 significantly increased the expression of TFAM, MTCO1 and PDH (p<0.05). Overexpression of miR-494 strongly decreased the oxygen consumption rate in 3T3-L1 beige cells and protein expression of PGC1-α and Ucp1 (p<0.05) in primary beige adipocytes. Finally, we explored the direct target of miR-494 and found that 3 UTR region of PGC1-α is a direct target of miR-494 by luciferase assay.

Conclusion: These findings demonstrate that miR-494 directly inhibits the expression of PGC1-α in adipose tissue. The decreased miR-494 expression during adipocyte differentiation removes its inhibitory effect, leading to stimulation of Ucp1 expression and mitochondrial biogenesis.
The Role of Glucagon-Like Peptide-1 for the Postprandial Effects of Metformin in Type 2 Diabetes

LAURA S. HANSEN, LÆRKE S. GASBJERG, ANDREAS BRÜNDEN, NiELS B. DALS-GAARD, EMILIE BAHNÉ, FERNILLE H. SØRENSEN, JENS J. HOLST, TINA VILT-BØLL, FILIP K. KNØP, Gentofte, Denmark, Copenhagen, Denmark, Hellerup, Denmark

Metformin is the most widely used drug for the treatment of type 2 diabetes. It has been shown that metformin increases plasma concentrations of glucagon-like peptide-1 (GLP-1), but it remains unknown whether metformin-induced GLP-1 secretion plays any role for the beneficial effects of metformin on postprandial glucose metabolism. We investigated the effect of metformin-induced GLP-1 secretion during meal ingestion in patients with type 2 diabetes using the GLP-1 receptor antagonist exendin(9-39). In a double-blinded, double dummy, placebo-controlled, randomized, cross-over study, 15 participants with type 2 diabetes (median age 71 years, BMI 30.07 kg/m², HbA1c 5.50 mmol/mol) were subjected to 14 days' metformin and placebo treatment, respectively, in randomized order with at least a 2-week washout period between treatments. At the end of each treatment period, two randomized 4-hour mixed meal tests with either concomitant exendin(9-39) (450 pmol/kg/min) or saline infusion, were carried out. Metformin treatment significantly lowered fasting plasma glucose and post-prandial plasma glucose excursions compared to placebo. We observed equal metformin-induced reductions in postprandial plasma glucose excursions during saline and exendin(9-39) infusions. Based on postprandial plasma glucose excursions, using the GLP-1 receptor antagonist exendin(9-39), we cannot confirm that GLP-1 secretion is involved in the beneficial postprandial glucose-lowering effects of metformin in patients with type 2 diabetes.

Supported By: National Institutes of Health (R01DK106191 to T.M.B.); JDRF (2-2012-280 to T.M.B.)

1967-P

Insulin-Like Growth-Factor Axis Collectively Identifies Pre-Type 1 Diabetes

MELANIE SHAPIRO, CLIVE WASSERFALL, ANDREW R. SCHULTZ, SEAN M. MCGRAIL, MICHAEL J. HALLER, DESMOND SCHATZ, MARK A. ATKINSON, TODD M. BRUSKO, Gentofte, Denmark

Somatostatin (SS) is a hormone inhibiting the secretion of the incretin hormone, glucagon-like peptide-1 (GLP-1) by binding to 5 SS receptors (SSTR). However, which SSTRs involved is still unclear. We hypothesized that antagonizing the SSTRs on enteroendocrine L-cells may increase secretion of GLP-1 and via GLP-1 receptor mediated mechanism lead to lowering of blood glucose. To investigate the level of the SSTRs we did expression analysis on L-cells isolated from throughout the murine intestine (n=3). We performed the proximal small intestine from mice (n=6-7) to investigate the levels were increased in AAbs (4.5 ± 4.0 ng/mL, p<0.01), and this was apparent in single AAbs+ FDR (79 ± 21 vs. 95 ± 22 ng/mL, p<0.05). Additionally, we established a multiple logistic regression model evaluating age, IGFs, and especially 5 had the highest expression on L-cells throughout the intestine. The SSTR2 antagonist resulted in an increase in GLP-1 secretion from 100nM, 5.82pM±0.7 p<0.0004; 15µM, 27.8µM±0.3 p<0.0004; 1µM, 19.7µM±1.2 p<0.0001; 10µM, 48µM±2.6 p<0.0001. Both SSTR2 and SSTR5 antagonists significantly reduced the blood glucose during an OGTT compared to the control (p=0.0006 and p=0.0072 respectively). This reduction in blood glucose was significantly increased when adding exendin(9-39) together with either the SSTR2 or 5 antagonist (p<0.0001 for SSTR2, p=0.0036 for SSTR5). Our results demonstrate that inhibiting the SSTR2 and SSTR5 increases GLP-1 secretion which in turn may cause the lowering in blood glucose during an OGTT.

Supported By: National Institutes of Health (R01DK106191 to M.A.A. and T.M.B.), ADA-Supported Research

1968-P

GLP-1 Secretion Is Increased upon Blockade of the Somatostatin Receptor Subtype 2 and 5 and Resulting in GLP-1 Receptor-Mediated Lowering of Blood Glucose in Mice

SARA L. JEPSEN, NICOLAI J. WEVER ALBRECHTSEN, JENS PEDERSEN, MAJA S. ENGELSTOFF, CAROLYN F. DEACONN, JENS J. HOLST, Copenhagen, Denmark, New York, NY

Somatostatin (SS) is a hormone inhibiting the secretion of the incretin hormone, glucagon-like peptide-1 (GLP-1) by binding to 5 SS receptors (SSTR). However, which SSTRs involved is still unclear. We hypothesized that antagonizing the SSTRs on enteroendocrine L-cells may increase secretion of GLP-1 and via GLP-1 receptor mediated mechanism lead to lowering of blood glucose. To investigate the level of the SSTRs we did expression analysis on L-cells isolated from throughout the murine intestine (n=3). We performed the proximal small intestine from mice (n=6-7) to investigate the impact of SSTR2 and 5 on GLP-1 secretion using intra-arterial administration of specific antagonists. Lastly we performed oral glucose tolerance tests (OGTT) on mice (n=8-9) after giving 1mg/ml SSTR2 or 5 antagonist with and without the GLP-1 receptor antagonist exendin(9-39) to investigate the role of these receptors on the glucose profile and to elucidate if their effect was mediated via GLP-1. The expression levels of the SSTRs showed that SSTR2 and especially 5 had the highest expression on L-cells throughout the intestinal tract. The SSTR2 antagonist resulted in a increase in GLP-1 secretion from the perfused intestine (100nM, 4.69µM±0.56, 1µM, 14.55µM±1.5; 1µM, 16.46µM±1.16; all p<0.0001). The same doses of SSTR5 antagonist gave a more potent GLP-1 secretion in this setup (100nM, 5.85µM±2.7; p=0.0004; 1µM, 19.79µM±1.2 p=0.0001; 10µM, 48µM±2.6 p<0.0001). Both SSTR2 and SSTR5 antagonists significantly reduced the blood glucose during an OGTT compared to the control (p=0.0006 and p=0.0072 respectively). This reduction in blood glucose was significantly increased when adding exendin(9-39) together with either the SSTR2 or 5 antagonist (p<0.0001 for SSTR2, p=0.0036 for SSTR5). Our results demonstrate that inhibiting the SSTR2 and SSTR5 increases GLP-1 secretion which in turn may cause the lowering in blood glucose during an OGTT.

Supported By: National Institutes of Health (R01DK106191 to M.A.A. and T.M.B.), ADA-Supported Research

1969-P

Exendin-4, but Not Oloxyylethanolamide, Promotes Host-Mediated Alterations to the Gut Microbiome during Weight Loss

JACOB BROWN, VANDANA SHARMA, DAVID TRAVN, SCOTT N. PETERSON, JULIO AVILA, Nashville, TN, La Jolla, CA

Gut-derived molecules like glucagon-like peptide-1 (GLP-1) and oloxyylethanolamide (OEA) are prime targets for developing more effective obesity therapeutics due to their weight loss action. Hypoglycemia is commonly cited as the mechanism by which OEA and Exendin-4 (Ex4), a GLP-1 receptor agonist, reduce body weight. However, we recently showed in diet-induced obese (DIO) mice that the hypoglycopic action of Ex4 and OEA is transient and that weight loss continues even as food intake returns to pre-treatment levels. This was associated with increased energy expenditure (EE) in Ex4+, but not OEA-treated, mice. Given the emerging role for the gut microbiome as a regulator of energy balance, we hypothesized that the long-term, food intake-independent weight loss elicited by Ex4 is associated with alterations in the gut microbiome. In vivo and in vitro experiments coupled with 16S analysis was used to determine the effect of chronic Ex4 and OEA on the gut microbiome during weight loss. Male, DIO C57/B6J mice (80% high-fat diet for 15 weeks) were dosed 2x daily with Vehicle, OEA (5mg/kg) or Ex4 (100µg/kg) for 7 days. Fecal pellets were collected pre- and post-treatment for 16S analysis. Ex4 caused a change (p<0.05) in 11 bacterial species, including a 5.6-fold increase in L. johnsonii, a bacteria that has been shown to improve metabolic outcomes in DIO models. In contrast, though Ex4 reduced body weight, OEA treatment had relatively little effect on the microbiome. To determine whether Ex4 and OEA directly alter the gut bacteria profile to promote weight loss, future experiments will determine if microbiome alterations contribute to the Ex4-mediated elevation in EE and improvements in metabolic outcomes.

Supported By: American Diabetes Association (1-14-CD-01 to J.A.J); National Institutes of Health (F32DK112663)

1970-P

In Insulin-Resistant Subjects, Ilet Functional Changes Might Represent an Attempt to Increase the Incretin Effect

TERESA MEZZA, SIMONA MOFFA, GIAN PIU SORCIE, CHIARA MARIA ASSUNTA CIFALO, FRANCESCA CINTI, ANDREA MARI, ANDREA GIACCARI, Rome, Italy, Padova, Italy

Nondiabetic insulin-resistant subjects (InsRes) display an increased α-cell mass, suggesting a key role of α-cells in the compensatory mechanisms to cope with insulin resistance states. The mechanism contributing to greater...
GLP-1 secretion detected in healthy patients following pancreatectoduodenectomy (PD), is not fully understood and suggests other potential sources of the incretin hormone, such as α-cells. To investigate the dynamic changes of in-vivo GLP-1 secretion, insulin secretion (IS), and incretin effect (IE), 16 nondonibiotic patients (10 F/6 M, 51±15 years.) scheduled for PD underwent a mixed meal test (MMT). A 2-h hyperglycemic clamp (HGC) and a hyperinsulinemic euglycemic clamp (IEC) before and after surgery. β-cell glucose sensitivity (GS) was calculated as the ratio of IS and glucose increments, both during HC and MMT. The IE was estimated as the ratio of GS during the HC and MMT. InsR displayed a reduction in the 1st IS at baseline (p=0.04), which did not decrease following PD. Both groups experienced a reduction of 2nd phase ISR (p<0.05 for both groups) and arginine-induced IS (p<0.05 for both groups) after surgery, with no difference observed in the reduction delta; while a significant reduction in basal ISR and GS was observed only in InsR after surgery (respectively p=0.03 and p=0.06). Following PD, GLP-1 secretion significantly increased in both groups (P<0.05 and P=0.02 respectively), but the percentage of increase was greater in InsR compared to insulin-sensitive subjects (InsSen) (respectively 54.4% vs. 36%). Further, the IE was significantly decreased in the InsSen (p=0.05), whereas no changes were observed in InsR. Our data suggest that acute islet mass reduction leads to different functional effects in InsR compared to InsSen. Impaired β-cell GS and reduced 1st IS are relatively compensated by preserved IE following PD in InsR. This may be driven by an increased α-cell mass in InsR, that might be the source of the increased GLP-1 secretion.

Supported By: European Foundation for the Study of Diabetes

1972-P
Association Between Body Fat Mass and Plasma Insulin Level in the Male Patients with Idiopathic Hypogonadotropic Hypogonadism and Normal Glucose Tolerance

XUHUA YANG, DONGDIAN LIN, XIANG HU, WEN XU, HONG R. DENG, Guangzhou, China

Male patients with idiopathic hypogonadotropic hypogonadism (IHH) characterized with low serum testosterone(T) might have higher risks of diabetes and coronary heart disease partly due to the high level of plasma insulin. Low serum T might also affect the body fat mass (BFM) in patients with IHH. However, the relationship between BFM and plasma insulin level in IHH patients has not been clearly clarified.

A total of 22 patients who were admitted to our hospital with IHH and normal glucose tolerance (NGT) confirmed by oral glucose tolerance test and 10 healthy subjects as controls were enrolled into our study. Glucose, insulin, serum T levels, HOMA-IR, HOMA-B and percentage of BFM were determined.

When compared with controls subjects, patients with IHH had significantly lower T concentrations (1.82nmol/L vs. 19.92nmol/L, P<0.001), whereas they had significantly higher BFM (31.38% vs.21.11%, P=0.004), fasting insulin level (15.88 mU/L vs. 7.65 mU/L, P=0.018), HOMA-B(23.19 vs. 120.26, P=0.016) and HOMA-IR(18.1 vs. 1.64, P=0.018). Pearson correlation revealed that BFM was correlated with fasting insulin level (r=0.83, P<0.002), HOMA-B(0.53, P=0.014) and HOMA-IR(r=0.47, P=0.031). Multiple linear regression revealed BFM was an independent factor of fasting insulin level (β=0.57, 95% CI:0.24~0.90, P=0.002), HOMA-B(β=0.096, 95% CI:0.01~0.18, P=0.030) and HOMA-IR(β=17.09, 95% CI:13.81~20.37, P=0.014).

BFM was an independent factor of plasma insulin level in IHH patients with NGT.

1975-P
Improvement of Insulin Resistance and Cardiovascular Risk Factors with Treatment of Subclinical Hypothyroidism in Patients with Autoimmune Thyroiditis

CELESTINO NEVES, SOFIA C. OLIVEIRA, JOÃO DER SEYES, MIGUEL G. PEREIRA, OKSANA SokhatSKA, ANA OLIVEIRA, JOSE LUIZ MEDINA, LUIS DELGADO, DAVIDE M CARVALHO, Porto, Portugal

Introduction: Subclinical hypothyroidism (SCH) seems to be associated with increase in cardiovascular risk factors and insulin resistance. The effect of the treatment of SCH with L-thyroxine on cardiovascular profile is not yet clear.

Methods: We evaluated the effects of L-thyroxine therapy in 120 patients (mean age 45.7±12.2 years, 80 women) with SCH due to autoimmune thyroiditis that had no prior treatment for thyroid or cardiovascular disease. The treatment was titrated to TSH levels between 0.4 and 4.0mU/L. The laboratory data obtained, before and at least 6 months after thyroid function normalization, included thyroid function, antithyroid antibodies, lipid profile, and HOMA-IR (Homeostasis Model Assessment for insulin resistance), HSI (Hepatic Insulin Sensitivity Index), and IGI (Insulinogenic Index). Statistical analysis was performed with Mann-Whitney test, and Spearman’s correlation coefficient.

Results: After L-thyroxine treatment, we observed a significant decrease of TSH (0.43±0.53 to 1.23±0.42 mU/L, p=0.03) and a significant increase of fT4 (0.74±0.12 to 1.25±0.14 ng/ml, p<0.05). We also observed a decrease of LDL (116.1±34.2 to 91.2±16.3 mg/dl, p<0.01) and Lp(a) (32.0±19.1 mg/dl, p<0.01). HDL and Apo A1 increased significantly after treatment (45.2±15.2 to 58.5±18.3 mg/dl, p<0.01; 124.5±43.3 vs. 136.5±56.4 mg/dl, p<0.01, respectively). Treatment with L-thyroxine significantly reduced HOMA-IR (0.24±0.17 to 0.17±0.10, p=0.03) and HSI (334.9±92.9 to 703.8±91.1, p=0.02). At baseline, TSH was positively correlated with total

Supported By: Ministry of Health of the Czech Republic (VFN64165, IN000023001)
cholesterol (r=0.38, p=0.01), LDL (r=0.38, p=0.01), TG (r=0.28, p=0.01) and IDI (r=0.22, p=0.05). FT3 was negatively correlated with Lp(a) (r=-0.41, p=0.04).

Conclusions: The treatment of SCH in patients with autoimmune thyroiditis is associated with a significant improvement of insulin resistance and cardiovascular risk.

**1976-P**

Iron Downregulates Leptin by Decreasing CREB O-GlcNAc Modification and CREB Occupancy of the Leptin Promoter

**JINGFANG LIU, YAN GAO, FELIPE LORENZO, SANDY T. SINK, DON MCCAIN, Winston-Salem, NC**

Modification of proteins by O-linked N-acetylgalactosamine (O-GlcNAc) serves as a nutrient-dependent signal to regulate transcription of the leptin gene. Recently we reported that increased levels of iron, which are also a risk factor for type 2 diabetes, downregulate leptin in mice fed high iron diets (2000 mg/kg) or in STZ1 cells treated with iron. Iron increased cyclic AMP-dependent response element binding protein (CREB) phosphorylation and its occupancy at inhibitory sites in the leptin promoter, but without demonstrable increases in CREB kinase activities. We now demonstrate that nutrient- and iron-dependent regulation of leptin are linked through O-GlcNAc modification of CREB. CREB O-GlcNAc modification was decreased in mice fed high iron, and this was associated with 54±7% and 44±5% reductions in recruitment to its two sites in the leptin promoter as analyzed by ChIP (p<0.05). Increasing levels of O-GlcNAc through targeted deletion of the O-GlcNAc (Oga) gene in adipocytes increased adipose leptin mRNA expression by 86±12% (p<0.05) in mice fed a low-normal iron diet (35 mg/kg) and partially rescued the effect of high iron (53±3%, p<0.05). Similar effects were seen in serum leptin levels: High iron caused a 72% decrease and OGA deletion rescued the decrease in a 34%. Treatment of STZ1 cells with iron decreased expression of a leptin reporter plasmid by 45±4% and glucosamine, which bypasses the rate-limiting step in synthesis of UDP-GlcNAc, the substrate for O-GlcNAcylation, increased protein O-GlcNAc and fully rescued the effect of high iron (p<0.001). Although iron also decreased global levels of protein O-GlcNAc modification, mRNA levels of the enzymes that control the modification, namely O-GlcNAc transferase and OGA, were unchanged. We conclude that adipose tissue integrates cellular nutrient status and tissue iron levels to control the regulation of leptin, through regulation of O-GlcNAc modification of the transcription factor CREB.

Supported By: National Institutes of Health; U.S. Department of Veterans Affairs

**1977-P**

The Family Coriobacteriaceae Is a Potential Contributor to the Beneficial Effects of Roux-en-Y Gastric Bypass on Type 2 Diabetes

**CHENG HU, WEIPING JIA, HAJUN LIU, Shanghai, China**

Background: Changes in gut microbiota induced by bariatric surgery have been associated with metabolic benefits. Objectives: Our aim was to identify specific gut microbiota that may contribute to the improvement of type 2 diabetes (T2D) after RYGB. Setting: Laboratories of Shanghai Diabetes Institute and Shanghai Sixth People’s Hospital. Methods: Diabetic rats induced via a high-fat diet and low-dose streptozotocin administration were randomized to RYGB or sham surgery (SHAM), and stool samples were collected at baseline and at postoperative week 8. The faecal microbiota was profiled using 16S ribosomal RNA (rRNA) gene sequencing. Additionally, we performed a case-control study of the gut microbial community profiles of T2D patients compared to those of healthy individuals (CONT) via 16S rRNA gene sequencing of mucosal-luminal interface samples collected from the ascending colon during colonoscopy. Results: RYGB significantly reduced the body weight and improved glucose tolerance and insulin sensitivity in diabetic rats. Principal coordinate analysis showed that RYGB caused marked alterations in the gut microbiota. The RYGB group was postoperatively enriched for Bacteroidetes, Proteobacteria, Fusobacteria and Actinobacteria; whereas the SHAM group was enriched for Firmicutes and Verrucomicrobia. Based on the gut microbial patterns in the T2D patients, we found that the family Coriobacteriaceae within Actinobacteria might contribute to the beneficial effects of RYGB on T2D. Conclusions: RYGB significantly improves glucose metabolism and alters the gut microbiota. Moreover, the family Coriobacteriaceae may partly mediate the beneficial effects of RYGB on T2D and thus possibly contribute to the development of novel bacteria-based therapeutic approaches.

ADA-Supported Research

**1978-P**

Glucagon-Receptor Signaling Regulates Mitochondrial Bioenergetics via Hepatic Farnesol X Receptor

**TEAYOUN KIM, SHELLY NASON, JESSICA P. ANTIPENKO, CATHERINA S. VESTRI, KELLEY SMITH-JOHNSTON, MARK E. PEFIN, ADAM R. WENDE, BRIAN FINAN, RICHARD DIMARCHI, DIEGO PEREZ-FELTIZE, DOUGLAS R. MOELLERING, KIRK M. HABECKER, Birmingham, AL; Helena, AL; Indianapolis, IN; Bloomington, IN; Cincinnati, OH**

Glucagon, an essential regulator of glucose and lipid metabolism, also promotes weight loss. We have identified that the hepatic Farnesol X Receptor (FXR) plays an important role in an anti-obesogenic effect of glucagon receptor (GoGR) agonism. Chronic administration of IUB288, a potent GoGR agonist, significantly reduced diet-induced obesity (DIO) in wild type (WT), 17% mice compared to (FXR/-/-, 6%) liver-specific FXR knock-out mice. Weight loss was associated with increased energy expenditure (p<0.05) and fat oxidation induced by RQ (p<0.05). We hypothesized that GoGR agonism alters mitochondrial bioenergetics, at least in part, through hepatic FXR signaling. IUB288 treatment increased body temperature (p<0.05) and [14C]-palmitate oxidation capacity of liver homogenate (p<0.05) to a greater extent in DIO WT mice than in FXR/-/- mice. RNA-Seq analysis of DIO liver samples revealed that the mitochondrial oxidative phosphorylation pathway, fatty acid metabolism, and bile acid metabolism were enriched in WT treated with IUB288, but not in FXR/-/- mice. Liver slices isolated from WT mice treated with IUB288 for two days significantly increased state 3 respiration rates compared to FXR/-/- mice using high resolution respirometry. Respiration was increased using both carnitine and long chain fatty acids (acylcarnitines, fatty acid oxidation inhibitors, and palmitoyl-carnitine), suggesting GoGR agonism modulates hepatic mitochondrial respiration via FXR. Our study elucidates a molecular mechanism of the anti-obesogenic effect of GoGR signaling. This heretofore-unappreciated aspect of glucagon biology has implications for the use of GoGR agonism in therapeutic strategies for multiple components of the metabolic syndrome. Supported By: National Institute of Diabetes and Digestive and Kidney Diseases (5U01DK048498; National Institutes of Health (R01DK12934)

**1979-P**

Peripheral Melanocortin 3 Receptor (MC3R) Regulates Haptic Autophagy in Obesity

**JOO YUN JUN, ARNOLD Y. SEO, TUSHAR P. PATEL, ANDREW J. UHLMAN, NOAH J. LEVI, ROBIN ROBERSON, JACK A. YANOFSKY, Bethesda, MD; Ashburn, VA**

We have previously reported homozgyosity for two MC3R SNPs (C17A+G241A) that partially inactive MC3R increases adiposity in humans and mouse models. However, the precise mechanisms by which hypoactive MC3R alters metabolic homeostasis remain unclear. Given the essential role of hepatic autophagy in cellular mechanisms of obesity, we hypothesized that diminished peripheral MC3R activity leads to hepatic lipid accumulation by interferring with autophagy, leading to steatosis. We used knock-in mouse models that carry either homozygous human “wild type” (MC3RWT/WT) or “double mutant” MC3R (C17A+G241A, MC3RΔΔ/ΔΔ). We studied hepatic autophagic pathways with biochemical/imaging analysis in wild type MC3R (C57/BL6) and MC3RΔΔ/ΔΔ as controls (WT mice), and in MC3RΔΔ/ΔΔ and mice lacking MC3R (MC3R−/−) which each have greater fat mass and hepatic triglycerides. We first demonstrated the MC3R specific agonist D-trp induced LC3II (a marker of autophagosome formation) in hepatocytes from WT, but not MC3R−/− or MC3RΔΔ/ΔΔ mice. Interestingly, the trp-α-SH agonist, significantly reduced diet-induced obesity (DIO) in wild type (WT, 17%) mice compared to (FXR−/−, 6%) liver-specific FXR knock-out mice. Weight loss was associated with increased energy expenditure (p<0.05) and fat oxidation induced RQ (p<0.05). We hypothesized that GoGR agonism alters mitochondrial bioenergetics, at least in part, through hepatic FXR signaling. IUB288 treatment increased body temperature (p<0.05) and [14C]-palmitate oxidation capacity of liver homogenate (p<0.05) to a greater extent in DIO WT mice than in FXR−/− mice. RNA-Seq analysis of DIO liver samples revealed that the mitochondrial oxidative phosphorylation pathway, fatty acid metabolism, and bile acid metabolism were enriched in WT treated with IUB288, but not in FXR−/− mice. Liver slices isolated from WT mice treated with IUB288 for two days significantly increased state 3 respiration rates compared to FXR−/− mice using high resolution respirometry. Respiration was increased using both carnitine and long chain fatty acids (acylcarnitines, fatty acid oxidation inhibitors, and palmitoyl-carnitine), suggesting GoGR-agonism modulates hepatic mitochondrial respiration via FXR. Our study elucidates a molecular mechanism of the anti-obesogenic effect of GoGR signaling. This heretofore-unappreciated aspect of glucagon biology has implications for the use of GoGR agonism in therapeutic strategies for multiple components of the metabolic syndrome. Supported By: National Institute of Diabetes and Digestive and Kidney Diseases (5U01DK048498; National Institutes of Health (R01DK12934)
OBESITY—ANIMAL

1980-P

Enterohemotropic Circulation of Bile Acids Is Activated by Bariatric Surgery before Weight Loss Becomes Apparent

YOSHIFUMI KITAMURA, KAZUHIKO KITAMURA, MAI HASUMURA, YUSUKE IWA, YORIKO OKAMATSU, Kawasaki, Japan

Bariatric surgery induces metabolic improvement before weight loss occurs. Plasma levels of bile acids (BA) are increased after bariatric surgery and this change is reported to contribute significantly to metabolic improvement. In this study, we investigated rats with duodenal-jejunal bypass (DJB) surgery to assess the mechanism underlying the increase in plasma BA after DJB surgery, especially before weight loss was detectable. Sprague-Dawley rats were fed a high-fat diet for 10 weeks and then were subjected to DJB surgery. Significant weight loss was noted in the DJB rats from 4 weeks after surgery. However, plasma triglycerides (TG) and the hepatic TG content were reduced at 2 weeks after surgery, although food intake was comparable between DJB rats and sham-operated rats. Plasma levels of total BA were elevated from 2 weeks after DJB surgery. In week 2, plasma levels of cholate and chenodeoxycholate were about 5-fold higher in DJB rats than in sham-operated rats, while cecal levels of both BA were lower in DJB rats compared with sham-operated rats. The increase in plasma BA was suppressed by administration of one of bile acid sequestrants, coleste-ride. Intestinal expression of BA transporters (ASBT, ABCB3, and OSto) was up-regulated in DJB rats, and hepatic expression of Cyp7a1 was also up-regulated in DJB rats at 2 weeks after surgery. These findings suggest that activation of de novo biosynthesis and increased enterohemotropic circula-
tion of BA contribute to elevation of plasma BA levels after DJB surgery before weight loss becomes apparent. These changes led to alteration of gut microbiota in DJB rats, and the resting core body temperature of DJB rats was increased over that of sham-operated rats from 2 weeks after sur-
gery. Therefore, elevation of plasma BA levels early after bariatric surgery by activation of de novo BA synthesis and enterohemotropic circulation may play an important role in postoperative metabolic improvement and weight loss.

1981-P

The Preprohormone Expression Profile of Enteroendocrine Cells following Roux-en-Y Gastric Bypass in Rats

LISE BIEHL RUDKJAER, CHEN ZHANG, KRISTOFFER RIGBOLT, SØREN L. PEDERSEN, MUNICHHEIDE FALKENHAIN, THOMAS HÜBSCHE, THORSTEN SCHMIDT, NIELS VRANG, JACOB JELSING, Hørsholm, Denmark, Fossendorf, Germany

It is well-known that Roux-en-Y gastric bypass (RYGB) leads to a rapid remission of type 2 diabetes and a marked and long-term body weight loss, but the molecular mechanisms driving these desirable effects are not fully understood. RYGB results in increased plasma levels of several gut peptide-hormones with either anorexigenic and/or antidiabetic effects. However, the potent effects of RYGB cannot solely be ascribed to these, and it is therefore likely that additional factors play a role. To gain further insight we have characterized the mRNA expression profile in enteroendocrine cells of the gut at day 9, 22 and 60 interaction surgery in a RYGB rat model. The enteroendocrine cells were identified by chromogranin-A immunohistochemistry staining, and isolated by laser capture microdissec-
tion from five locations covering the full rostrocaudal extent of the gastrointestinal tract. The mRNA expression profiles were analyzed by RNAseq, and bioinformatic analyses were applied to identify known and predicted preprohormones differentially regulated following RYGB. In total 64 putative preprohormones were identified in the secretome of rat enteroecrine cells, of which 40 were shown to be differentially regulated at one or more time-points post surgery, including several well-known preprohormone genes (GCG, CCK, GHRH, GIP, NMU, SFT, NPY, and VIP). Only six preprohor-
mones were differentially regulated at all time-points (NMU, TAC, FM3D, SFT, C1, and ADM). We present the full mRNA expression profile of the secretome of chromogranin-A positive enteroendocrine cells following RYGB surgery in rats. The data provides a region-specific characterization of all preprohormone encoding genes in the rat gut, including 23 not hitherto known. This comprehensive catalogue of gut peptide hormone expression might help our understanding of hormone mediated effects of RYGB on diabetes remission and body weight lowering.

1982-P

APPL2 Promotes Inflammation in Mouse Liver by Negative Regulation of Adiponectin Signaling

JYOUN RVU, San Antonio, TX

Adiponectin is an insulin sensitizer that exerts anti-diabetes and anti-
flammation functions. Adiponectin signaling is negatively regulated by the adaptor protein APPL2 in cells, yet it has roles in APPL2 remains largely unknown. In this study, we show that liver-specific knockout of APPL2 improved insulin sensitivity and enhanced adiponectin signaling in high-fat diet (HFD)-fed mice. The liver-specific APPL2 knockout mice (APPL2−/−) had less macrophage infiltration in liver tissues compared with their wild-type controls and were resistant to LPS-induced expression of inflamma-
tory genes such as IL-6, IL-1α, MCP-1, and TNF-α. Pretreatment of macro-
phage Raw264.7 cells with conditioned media from primary hepatocytes of APPL2−/− mice attenuated LPS-stimulated expression of inflammatory genes and the migration of the cells. The anti-inflammatory effect of APPL2 knock-
out was significantly reduced in adiponectin and liver-specific APPL2 double knockout mice (Adiponectin−/−/APPL2−/−). Taken together, our results show that APPL2 promotes inflammation in mouse liver and the protein exerts a pro-inflammatory role by antagonizing adiponectin signaling.

1983-P

The Regulation of BRD7 in the Insulin Signaling Pathway

SANG PARK, YOUNGHAH HAN, MARIO A. SALAZAR HERNANDEZ, Boston, MA

Endothelial cell proliferation (ECPI) is an essential step during the development of insulin resistance, type 2 diabetes, and obesity. BRD7, X-box binding protein 1 (XBPI) is one of the master regulators of ER folding function and is involved in the regulation of ER stress. We activated the expression of XBPI led to the development of obesity, insulin resistance, and type 2 diabetes in mice in a background that is resistant to the development of obesity. To date, our understanding of the regulation of XBPI in metabolic processes is still limited. In our previous work, we demonstrated that bromodomain containing protein 7 (BRD7) regulates glucose homeostasis by increasing the nuclear translocation of XBPIs through its interaction with the regulatory subunits of phosphatidylinositol 3-kinase (P3K, p85). We also showed that BRD7 protein levels are significantly reduced in the liver of genetically obese ob/ob and high fat diet (HFD)-induced obese mouse models, and over-expression of BRD7 in the liver of ob/ob and HFD fed mice ameliorates hyperglycemia and glucose intolerance through increasing the activity of XBPI. In our current unpublished work, we show that BRD7 heterozygous knockout mice are prone to developing obesity when they are challenged with a HFD. They display increased hepatic triglyceride levels with moderately severe steato-
sis. In addition, we generated a liver-specific BRD7 knockout mouse model (LBRD7) to examine the effect of BRD7 specifically in the liver. LBRD7 mice fed on a HFD exhibit increased body weight compared to their wild type control mice. Downregulation of BRD7 in the liver led to lack of nuclear XBPIs in the liver in both the knockout mouse model and adenovirus-mediated knock-
down system. Our results provide the first evidence that BRD7, which had originally reported as a tumor suppressor, is involved in the development of obesity as well as in the regulation of unfolded protein response (UPR) and glucose metabolism.

Supported By: American Diabetes Association (1-17-IBS-104 to S.P.) National Institutes of Health

1984-P

The Transcription Factor ETV5 Regulates Adipogenesis through PPARγ Signaling Pathway

ZHUO MAO, Shenzhen, China

ETV5 is a member of PEA3 subfamily of E2F transformation-specific (ETS) transcription factors, characterized by the conserved DNA binding domain, ETS domain. Recently, a series of genomic-wide association studies (GWAS) found that ETV5 is associated with obesity. ETV5 knockout mice have lower fat mass and resistant to diet induced obesity, suggesting it was involved in the adipogenesis. In our study, we showed that ETV5 was expressed in the nucleus of adipocyte. In the current study, we examined its expression level after dieting in mice resided with high fat diet. At 4 weeks after surgery, the expression of ETV5 was significantly elevated during adipogenesis. We utilized lentivirus to successfully knockdown ETV5 in 3T3-L1 cells. Deficiency of ETV5 resulted in reduced number and smaller size of adipocytes showed by oil red O staining. The major genetic changes involved in the impaired adipogenesis was defective PPAR signaling. Rosiglitazone stimulation of 3T3-L1 could restore adipogenesis caused by ETV5 deficiency.
Dual luciferase assay found that ETVs potentially enhanced PPRE activity. These results suggest ETVs is an important regulator of adipogenesis in early stage and a potential target for the treatment of obesity.

**Supported By:** National Science Foundation of China (51500819) and Aozang Medical-Tech Co., Ltd.

**Endothelial ULK1 Regulates High-Fat Diet-Induced Obesity via FGF-21**

MANNAN LI, MING QIAN, JIAN XU, OKLAHOMA CITY, OK

Fibroblast growth factor (FGF) 21 is a hormone with huge potential for pharmaceutical development for treatment of metabolic disease. The role of endothelial cell (EC)-derived FGF-21 in obesity remains largely unknown. Although we detected lower EC-FFG-21 levels in visceral fat of Ob/Ob and high-fat diet (HFD)-fed mice than the control lean mice. This study was to identify the role and mechanism of EC-FFG-21 in HFD-induced obesity using cell culture and mouse models. Mimicking HFD, long-term incubation with palmitate (100 μM, 16h) reduced FGF-21 levels in HUVEC that were co-cultured with 3T3-L1- adipocytes. The reduction was prevented in ULK1-siRNA treated HUVEC, via AT1F4-promoted mRNA expression and increased protein stability of FGF-21. Thus, FGF-21-induced expression of FGF-R1c, β-Klotho, UCP1 and GLUT1 was enhanced in co-cultured adipocytes. To confirm these findings in vivo, we used a Tie2-Cre-lox to generate mice with EC-knockout of FGF-21 (FKO), ULK1 (UKO), or both (DKO). In 8-to-10-week-old male mice (n=15-20/group) fed an HFD (Text: diet: 60% energy from fat) for 3 weeks, wild type (WT, C57BL/6J) mice developed obesity and insulin resistance, which was worsened in KKO mice. In contrast, KKO mice gained less body weight and visceral fat mass and had improved glucose tolerance, with significant differences in food and water intake. Levels of adipose tissue EC-FFG-21 was normalized in UKO mice, as determined by immunohistochemistry of FGF-21 and EC markers (CD31 and lectin). Expression of adipose tissue FGF-21, β-Klotho, UCP1, and GLUT1 was restored in UKO, but not WT, mice. Concomitant with UCP1 induction, the visceral fat showed beige-cell-like deposits with fewer expanded adipocytes. However, this favorable phenotype was absent in DKO mice.

In summary, EC-ULK1 mediated HFD-induced obesity and insulin resistance through loss of EC-FFG-21, at least in part, by blunting local FGF-21-signaling in adipose tissue. Therapeutic targeting of the EC-ULK1-FFG-21 pathway may be a new treatment for obesity and insulin resistance.

**Supported By:** American Diabetes Association (1-12-JF-58 to J.K), National Institutes of Health, Oklahoma Center for the Advancement of Science and Technology, Public Health Foundation, American Heart Association

**Vitamin D3 Alleviates High-Fat Diet-Induced Endoplasmic Reticulum Stress and Insulin Resistance in Mice**

LI LIU, XIAOHUA LI, SHANGHAI, China

Endoplasmic reticulum stress (ERS) may be a key mechanism for the connection of obesity, chronic inflammation, and insulin resistance (IR). As we know, vitamin D3 deficiency is prevalent in obese patients, and it may be an independent risk factor for obesity-induced IR and type 2 diabetes mellitus (T2DM). However, the effects of vitamin D3 on ERs, inflammatory response, and IR were still unknown. This study investigates the effects of vitamin D3 on ERs, inflammatory response, and IR in high-fat-diet (HFD) induced obese mice. Eight male C57BL/6J mice were randomly divided into four groups: control group (n = 20), HFD group, HFD + low dose (50 IU/kg) of vitamin D3 group (VitD-L), HFD + high dose (250 IU/kg) of vitamin D3 group (VitD-H). The control group was fed with common feed, and the other groups were fed with HFD. After the establishment of the obesity model, the mice in experimental group was fed with different dose of vitamin D3 for 1 week. Then western blot was used to detect the protein expression level of BIP, IRE1, PERK and NF-κB in adipose tissue; serum levels of TNF-α, IL-6, serum 25-hydroxyvitamin D3, fasting blood glucose, glycosylated hemoglobin, triacylglyceride and fasting insulin were measured and the insulin resistance index was calculated. The results indicated that vitamin D3 in both low and high dose could significantly down-regulate the expression level of BIP, IRE1 and PERK, and decrease the expression levels of NF-κB, TNF-α, and IL-6 (p < 0.05). It could also significantly decrease the levels of fasting blood glucose, glycosylated hemoglobin, triacylglyceride and fasting insulin in obese mice (p < 0.05), and significantly alleviate the insulin resistance phenomenon in obese mice. The results indicated that vitamin D3 supplementation could reduce the synthesis and release of inflammatory factors, elevate endoplasmic reticulum stress and insulin resistance.

**Supported By:** Shanghai Municipal Health and Family Planning Commission.

**Endothelial Hydrochloride Protects Cytokine-Induced Inflammation Through Multiple Pathways**

ANIL PUILDE, JOSEPH ZHOU, SCOTT MASSEY, LIXIN LI, AUCL, MOUNT PEACEANT, AL, LAKE ISABELLA, MI

Berberine hydrochloride (BBR) has been reported to improve insulin resistance. However, the underlying mechanism remains largely elusive. We therefore investigate the anti-inflammatory role of BBR and the cell signaling pathways that involved.

C2C12 myoblasts were treated with L-1P (10mg/ml) alone or in combination with TNF-α (5ng/ml) in the presence or absence of BBR (10 μM) for 24 hours. Western blot analysis was used to assess the protein level. In vivo study is conducted using C57Bl/6J mice fed with high fat high sucrose (HFHS) diet to induce insulin resistance. Skeletal muscle was collected after 4 weeks treatment with either 5 mg/kg BBR or vehicle.

BBR reduced activity of INOS, and stress-related kinases, including p38 MAPK, NF-κB, SAP/JNK, MKK4 and J-CUN that was induced by cytokines in C2C12 myoblasts. Furthermore, BBR reversed cytokine mediated suppression of AMPK-α, augmented activity of SIRT-1 and PGC-1α. Antioxidant enzyme or transcription factor, nuclear factor like 2 (NRF-2) were also elevated after BBR treatment. In addition, BBR improved insulin signaling in C2C12 myoblasts.

HFHS diet induced iNOS expression was reversed by BBR in skeletal muscle. Activation of the activity of uncoupled protein-3 (UCP-3) and PPARα in HFHS diet skeletal muscle was observed.

Our results demonstrate that BBR alleviates cytokine induced inflammation and oxidative stress. BBR improves mitochondrial function, promotes insulin sensitivity. The anti-inflammatory effect of BBR in skeletal muscle may mediate through multiple pathways including activation of AMPKα-SIRT-1-PGC-1α pathway, and inhibition of MKK4- SAP/JUNK-C-JUN pathway. BBR is a potential medication in treating obesity induced insulin resistance.

**Supported By:** Central Michigan University
Loss of Fractalkine-CX3CR1 Signaling Exacerbates Obesity-Induced Adipose Tissue Inflammation and Insulin Resistance through M1 Dominant Shift in Macrophages

MAYUMI NAGASHIMA, YINHUA NI, TSUGUHITO OTA, Kanazawa, Japan

Adipose tissue macrophages (ATMs) accumulation through CCR2 and its ligand MCP-1 is considered pivotal in the development of insulin resistance. Recently, we found that CX3Cl chemokine, fractalkine (CX3CR1) mRNA expression was persistently downregulated in epididymal white adipose tissue (eWAT) of HF diet (HFD)-induced obese (DIO) mice, as compared to lean controls. Furthermore, we demonstrated that loss of fractalkine receptor, CX3CR1, exacerbated HFD-induced insulin resistance and glucose intolerance. Here, we show that fractalkine-CX3CR1 signaling plays a crucial role in the inflammatory response to HF feeding by regulating macrophage M1/M2 status. To determine the effect of fractalkine-CX3CR1 signaling on ATM subsets, we performed flow cytometry analysis to quantify M1/M2 ATMs in eWAT of CX3CR1⁻/⁻ (KO) and WT mice. Immunofluorescence studyline shown as DIO mice revealed that CX3CR1 was predominantly expressed by F4/80⁺ macrophages in crown-like structures (CLS). On an HFD, KO mice had increased macrophage infiltration and formation of CLS in eWAT compared with those of WT mice, despite that weight and adipocyte size were similar. KO mice had 40% or 39% more CD11c⁺CD206⁻ (M1) ATMs on normal chow (NC) or HFD, and 17% or 49% fewer CD11c⁺CD206⁺ (M2) ATMs on NC or HFD, respectively, than WT mice, resulting in predominance of the M1 over M2 ATM population. Furthermore, the predominance of the Ly6C⁺ over the Ly6C⁻ monocyte fraction was observed in the peripheral blood and bone marrow (BM) of KO mice on NC or HFD. Importantly, HFD-induced adipose inflammation and hyperinsulinemia were aggravated in chimeric mice lacking CX3CR1 only in myeloid cells (BM transplant of KO to WT) as compared to control mice (BM transplant of WT to WT). Thus, loss of fractalkine-CX3CR1 signaling causes M1 dominant phenotypic shift in ATMs, which contributes to exacerbation of obesity-induced adipose tissue inflammation and insulin resistance. Supported By: Japan Ministry of Education, Culture, Sports, Science and Technology

Glycolytic Activation Promotes PDGF-B Production in Adipose Tissue Macrophages during Obesity Development

YASUHIRO ONOGI, TSOTOMU WADA, TAKATOSHI MATSUZAWA, AKIRA OKEKAWA, ERI WATANABE, HIROSHI TSUNEKI, TOSHIYASU SASAOKA, Toyama, Japan

The vascular network develops with remodeling in adipose tissue (AT) during obesity. We have found that PDGF-B detaches pericytes from the vasculature, which plays a crucial role in angiogenesis during obesity. The expression of PDGF-B was significantly elevated in obesity-associated infiltrated CD11c-positive (+) AT macrophages (ATMs). Interestingly, the expression was low in both CD11c⁺ ATMs and CD206⁺ ATMs of lean mice. Since glycolytic and oxidative metabolism are key metabolic programs that regulate ATMs’ polarity and function, we hypothesized that hyperglycemia and inflammation synergistically drive PDGF-B production by reprogramming metabolic pathways in ATMs. The expression of PDGF-B was increased in the AT of high-fat-diet (HFD)-fed mice and STZ-induced hyperglycemic mice. In accordance, exposure to high glucose led to increase the expression of PDGF-B in association with that of Ifg6 (CD11c) in RAW264.7 macrophages. In peritoneal macrophages, LPS but not IL-4 provoked PDGF-B expression, which was completely blocked by pretreatment with 2-DG, a glycolysis inhibitor. Moreover, LPS effectively augmented high glucose-induced its expression, and that was abolished by MG132, an NFκB inhibitor. Since macrophages highly accumulated in obese AT, where pericytes were detached from vasculature, we examined directly whether PDGF-B from macrophage involves in AT expansion during obesity. To this end, we intraperitoneally injected liposome-encapsulated clodronate (CL) to mice twice a week for 6 weeks during HFD feeding. ATMs were effectively depleted by CL with reduced PDGF-B expression in AT of HFD-induced obese mice. Importantly, HFD-induced obesity was effectively prevented by CL. In conclusion, PDGF-B from ATMs has a crucial function in AT expansion during obesity. Hyperglycemia and chronic inflammation reprogram metabolic pathways toward glycolysis, and subsequent activation of NFκB plays a pivotal role in the production of PDGF-B in ATMs during obesity.
Deficiency of Melanocortin 4 Receptor Promotes Vascular Vulnerability in Mice

KENTARO MORI, KYOICHIRO TSUCHIYA, SUGURU NAKAMURA, YASUTAKA MIYACHI, KUMIKI SHIBA, YOSHITHD TIGAWA, KENICHIRO KITAMURA, CHOU, Japan, KOEI, Japan, PIKU, Japan, FUKUSHIMA, Japan

Background: Obesity is known as a risk factor of hypertension and abdominal aortic aneurysm (AAA) in humans. Melanocortin 4 receptor (MC4R) is primarily expressed in brain, and mediates most of the anorectic effects of leptin, in humans, deficiency or mutation of MC4R is the most common monogenic form of obesity. However, it remains unknown whether MC4R signaling affects the development of obesity-associated hypertension, vascular vulnerability and aortic aneurysm.

Methods and Results: MC4R-knockout (KO) mice fed a high-fat/high-sucrose diet (HF/HS) for 20 weeks displayed obesity and insulin resistance associated with hyperleptinemia compared to HF/HS-fed wild type mice. HF/HS-fed MC4R-KO mice exhibited hypertension, and showed increase of medial thickness and elastic lamina destruction in aortae. In aortae of HF/HS-fed MC4R-KO mice, genes of MCP-1, TNF-α, and F4/80 were markedly upregulated relative to HF/HS-fed wild type mice. Following the administration of angiotensin II (Ang II, 500 ng/kg/min), HF/HS-fed MC4R-KO mice showed significantly lower survival rate and higher incidence of AAA than HF/HS-fed wild type mice, with increased expression of F4/80- and osteopontin-positive cells in aortae. Furthermore, HF/HS-fed ob/ob mice exhibited significantly lower incidence of Ang II-induced AAA with a trend of higher survival rate than HF/HS-fed MC4R-KO mice. Leptin (100 ng/ml) significantly upregulated osteopontin gene expression in primary cultured vascular smooth muscle cells (VSMCs), but not in primary cultured macrophages. Conclusion: Our observation clearly demonstrates that deficiency of melanocortin 4 receptor promotes the development of hypertension, vascular vulnerability, and Ang II-induced AAA in mice. It also suggests that hyperleptinemia caused by central leptin resistance could contribute to the development of these vascular phenotypes in MC4R-KO mice, at least partly via induction of osteopontin in VSMCs.

ILDR2 Alters Hepatic Phospholipid Composition via MBOAT7—Effects on Liver Fat

KAZUHIRO KAZUHIRO WATANABE, KEN TOSHIYUKI KANDA, ELIZABETH J. MILLING, CHARLES A. LEDUC, ROUDULPH LEBEL, SADAHIKO IWAMOTO, SHIMOTAKE, Japan, KASHIWA, Japan, TOCHIJI, Japan, ATLANTA, GA, New York, NY

Nonalcoholic fatty liver disease (NAFLD) is associated with obesity and type 2 diabetes, and increases the risk for liver cirrhosis and cancer. A diabetes susceptibility gene, ILDR2, encodes a transmembrane protein localized to the ER membrane whose primary physiological functions are unclear. We previously purified ILDR2-containing protein complexes using the tandem affinity purification tags and identified MBOAT7, which mediates acyl-chain remodeling of phosphatidylinositols (PtdIns). The MBOAT7 variant rs641738 T allele is associated with decreased hepatic PI (36:4) and PI (36:3) and an increased severity of NAFLD. We hypothesized that ILDR2 may influence hepatic PI composition in NAFLD. We used two mouse models fed a methionine- and choline-deficient (MCD) diet: 1.) liver-specific ILDR2 knockout (LKO-ILDR2) mice and subcutaneous fat. Lipogenesis was reduced in visceral WAT but elevated in subcutaneous fat via the tissue-specific modulation of lipid metabolism and stimulation of subcutaneous white adipose tissue (WAT) browning. We showed that liraglutide decreased visceral fat and relatively increased subcutaneous fat. Lipogenesis was reduced in visceral WAT but elevated in subcutaneous WAT treated with liraglutide. Lipolysis was also attenuated, and fatty acid oxidation was enhanced. The mRNA expression levels of adipose-related genes displayed similar trends. Liraglutide down-regulated the expression levels of lipogenesis- and lipolysis-related genes but up-regulated the expression levels of β-oxidation-related genes in visceral WAT. In subcutaneous WAT, the expression levels of lipogenesis-related genes were up-regulated in both inguinal and clunal WAT. However, the lipolysis-related gene expressed higher in inguinal WAT but lower in clunal WAT, while the β-oxidation-related gene expressed lower in inguinal WAT but higher in clunal WAT after liraglutide treatment. In addition, the uncoupling protein-1 was up-regulated in subcutaneous WAT. Thus, liraglutide potentially redistributes body fat and promotes browning remodeling in subcutaneous WAT to improve metabolic disorders.

Supported By: National Natural Science Foundation of China; Science and Technology Commission of Shanghai Municipal Government; Shanghai Municipal Commission of Health and Family Planning
characteristics of ICA6150349 were also determined. In rats, there was a pharmacologically expected dose-dependent decrease in body weight (BW) gains and food consumption, which demonstrated a recovery trend. Clinical pathology and anatomic pathological changes, largely restricted to the exogastric pancreatic effect of glucagon at high exposures, had mostly recovered during the dose-free period. ICA6150349 exposures (AUC0–6) increased dose-proportionally in male and female rats on D2. On D14, exposure was 40-60% lower than on D2 in the 0.875 and 8.75 mcg/day dose groups and similar to D2 in the 87.5 mcg/day dose group after adjustment for changes in BW. ADAIs were observed in rats from all dose groups, but did not impact the TK of ICA6150349. In cynomolgus monkeys, the effects of ICA6150349 were limited to minimally decreased RBC mass (hemoglobin, red blood cell count, and hematocrit) at 3584 mcg/day with recovery. ICA6150349 exposure (AUC0–6) increased dose-proportionally on D2. On Day 14, exposures were 14-65% lower than on D2 in all groups except the 3584 mcg/day females. ADA were observed in 46.7% of treated monkeys; however, ADA status only affected TK at the 3584 mcg/day dose level. Overall, ICA6150349 was well tolerated. Nonclinical safety studies identified no adverse effects (based on the minimal magnitude of change, severity grading and reversibility) at any dose level tested with a NOAEL of 87.5 mcg/day in rats and 3584 mcg/day in monkeys. All observed effects have been non-adverse, reversible, and consistent with known actions of glucagon.

IC6150349, a Highly Selective Glucagon Agonist, in Combination with Exenatide Significantly Reduces Weight and Glucose in Obese and Diabetic Rats

MARK PAULIK, TOM TLUSTY, MARY K. GRIZZLE, MARCI COPELAND, SHARON WENG, WILLIAM C. BLACKWELL III, VED SRIVASTAVA, JAMES WAY, SHANE ROLLER, DORIS ZANE, REBECCA HODGE, ANDREW A. YOUNG, PAUL L. FELDMAN, Research Triangle Park, NC; Durham, NC; Hayward, CA

IC6150349, a 38-amino acid analog of glucagon, is peptidase resistant and highly selective for the glucagon receptor. ICA6150349 continuously infused SC at 50 mcg/kg/d (ED50) in DIO LE rats reduced weight (21%), fat mass (37%), and food intake (17%) and normalized triglycerides and cholesterol to lean control levels. ICA6150349 (50 mcg/kg/d) in combination with exenatide (10 mcg/kg/d) further reduced weight (38%), fat mass (70%), and food intake (52%) and also normalized glucose and lipids to lean control levels. ICA6150349 continuously infused at 50 mcg/kg/d in ZDF rats increased food intake (52%) and also normalized glucose and lipids to lean control levels. ICA6150349 continuously infused at 50 mcg/kg/d in combination with exenatide (10 mcg/kg/d) decreased HbA1c (1.3%), reduced weight (29%), fat mass (42%), and food intake (13%) and normalized triglycerides (66%) and cholesterol (38%) to lean control levels. ICA6150349 (50 mcg/kg/d) in combination with exenatide (10 mcg/kg/d) decreased HbA1c (1.5%), off-setting the increase seen with ICA6150349 monotherapy. The IC6150349 and exenatide combination reduced weight (19%), fat mass (25%), food intake (29%) cholesterol (27%) and triglycerides (41%). In rodent models of obesity/2D, ICA6150349 in combination with exenatide can significantly reduce weight, fat mass, glucose and lipids, sometimes normalizing these parameters to lean control levels.

Figure 1: Dose Effects of IC6150349 (10 mcg/kg/d) and Exenatide (5 mcg/kg/d) on Body Weight in DIO LE Male and Female Rats (A) and Food Intake (B) and Activity (C).

Supported By: National Institutes of Health (SU2C-DK093000)

PBI-4547 Reverses Diabetes and Metabolic Syndrome through Regulation of Lipid/Glucose Metabolism, β-Oxidation and Fibrosis in Liver, and White Adipose Tissue in ob/ob Mice

LYNE GAYNON, ALEXANDRE LAVENDER, FRANCOIS SARRA-BOURJET, MARIE-PER COUTURIER, ALEXANDRA FELTON, MIKAEL TREMBLAY, JONATHAN RICHARD, LIETTE GERVais, PIERRE LAURIN, FRANCOIS A. LEBLOND, BRIGITTE GROUIX, Laval, QC, Canada

Introduction and Aims: Given the expected rise in the prevalence of obesity and type 2 diabetes, hepatic steatosis will, if not already, become an epidemic. The aim of this study was to determine the mechanism of action of PBI-4547 on diabetic complications.

Methods: ob/ob mice (6 weeks old) were treated with vehicle or PBI-4547 (10, 25 and 50 mg/kg, oral once a day) from day 1 through 105. Liver and white adipose tissue (WAT) histology, blood glucose, serum triglyceride and adiponectin levels were examined. Gene expression of pro-inflammatory/fibrotic markers, metabolic and mitochondrial fatty acid transport and oxidation (FAO) regulators, and PPAR gene expression were determined in liver and WAT.

Results: Blood glucose, cholesterol and triglyceride levels were strongly reduced by PBI-4547. ob/ob mice displayed severe liver steatosis which was completely reversed with PBI-4547. PBI-4547 significantly reduced fibrosis, inflammatory cell infiltration, and adipocyte size in WAT. Serum level of adiponectin was reduced in ob/ob mice and increased with PBI-4547. In liver, PBI-4547 reduced TNF-α, collagen I, III and IV, α-SMA, fibronectin, MMP-2, TIMP1, ICAM, PDGFα, TGFβ1, PPARα and PPARγ, but increased mitochondrial FA transport and oxidation (ACOX-1, CD36, FABP4, CPT1β, PDH4). In WAT, PBI-4547 reduced TNF-α, collagen types I, V and W, MMP-2, MCP-1, F4/80, increased PPARγ and PPARα, and also increased ACOX-1, CD36, FABP4, PDX1, SREBF1, PGC-1α, UCP-1 (by 160X, suggesting browning of adipose tissue), CPT1α, CPT1β and PDH4. Furthermore, PBI-4547 increased adiponectin and its receptors, and abolished vasin gene expression.
Conclusions: PBI-4547 is a potential novel therapy for diabetes and hepatic steatosis through its pleiotropic activities on glycogen and lipid metabolism, by improving mitochondrial dysfunction, by inducing browning of adipose tissue, and by regulating adipokines.

2001-P

Obesity-Associated Family with Sequence Similarity 13 Member A Gene Regulates Adipocyte Differentiation

JIAZHENG TANG, HONGYI ZHOU, JING YANG, WEIQIN CHEN, Nanchang, China, August, GA, Urbana, IL.

Obesity and its associated morbidities represent the major and most rapidly expanding health epidemic in the world. Recent genome-wide association studies (GWAS) have identified single nucleotide polymorphism (SNP) variants in Family with Sequence Similarity 13, Member A (FAM13A) gene to be highly associated with waist-hip ratio (WHR) with adjustment for body mass index (BMI) (NHRRadBMI). However, the exact function of this gene in adipose tissue development and obesity remains largely uncharacterized.

We for the first time identified FAM13A as an adipocyte tissue abundant gene whose expression was highly regulated by fasting/refeed and dramatically reduced in epididymal and subcutaneous fat depots in murine models of genetic obesity and diet-induced obesity (DIO). Its expression was enriched in mature adipocytes and significantly upregulated during murine and human adipogenesis potentially through a PPARα-dependent mechanism. However, FAM13A-/- mice only exhibited a tendency of higher adiposity and maintained normal glucose clearance and insulin resistance. They are also not protected from high fat diet-induced obesity and metabolic perturbation.

The dispensable role of FAM13A was further supported by normal adipogenesis in FAM13A-/- Stromal vascular cells (SVCs). Interestingly, overexpression of FAM13A in 3T3-L1 preadipocytes downregulated beta-catenin expression, impaired preadipocyte survival and enhanced its susceptibility to serum starvation-induced apoptosis. Furthermore, FAM13A-overexpressing preadipocytes failed to differentiate into mature adipocytes through interfering early-stage C/EBPα/PPAR-mediated adipogenesis. These data for the first time reveal new details of an obesity-associated FAM13A gene in mediating beta-catenin action and adipocyte differentiation, providing novel insight into a relationship between FAM13A and adipocyte biology.

Supported By: National Institutes of Health; American Heart Association

2002-P

Small Proliferative Adipocytes, Newly Identified Adipose Progenitor, as the Precursores of Beige Cells

KOICHIRO TAGUCHI, KAZUO KAJITA, MASAYUKI FUWA, MUTODHIKA ASANO, YOSHINISHI KITADA, TAKAHIDE IKEDA, TATSUO ISHIKURA, HIROYUKI MORITA, Gifu, Japan

We previously identified proliferative cells in adipose tissue expressing adipocyte-specific genes and preadipocyte specific genes, which were named small proliferative adipocytes (SPA). Furthermore, we found that SPA specifically express prolin (PLF) and have superior potential for adipogenic differentiation as compared to stromal vascular cells (SVCs). In this study, we investigated the role of SPA. A comparison between differentiated SPA (D-SPA) and differentiated SVC (D-SVC) revealed that UCP1 and PLF were strongly expressed in D-SPA. Therefore, we speculated that SPA might be progenitor of beige cells. The real time PCR analyses and the immunohistochemical studies revealed that beige cells associated genes, including UCP1, FABP4a and PGC1α were significantly increased in D-SPA. Treatment with pioglitazone and CL316243, a specific α3-adrenergic receptor agonist, converted cultured SPA into cell clusters like beige cells which expressed UCP1 and activation of mitochondrial function confirmed by MitoRed stain. Furthermore, PLF was expressed in beige cells induced by continuous injection of CL316243.

In conclusion, since D-SPA were found to express UCP1 and PLF, which were detected in beige cells, but not VAT, SPA were considered to be a progenitor of beige cells. There might be two lineages of cells in adipose tissue; adipose progenitor cells in SVC and VAT (PLF-); and SPA and beige cells (PLF+). The combination of pigilastone and CL316423 produced an additive effect of inducing browning in SPA.

2003-P

Self-Assembled Hyaluronic Acid Nanoparticles Ameliorate Adipose Tissue Inflammation and Insulin Resistance in Diet-Induced Obese Mice

JUN YI RHO, WANGHEE LEE, EUNYOUNG LEE, CHONGYI KIM, EUN KYUNG LEE, WOOK KIM, Suwon, Republic of Korea, Seoul, Republic of Korea

Self-assembled hyaluronic acid nanoparticles (HA-NPs), consisting of hydrophobic cores surrounded by a hydrophilic HA shell, have been extensively investigated for biomedical and pharmaceutical applications because of their biocompatibility and receptor-binding properties. Here, we report that an empty HA-NP itself not bearing any drug has therapeutic effects on adipose tissue inflammation and insulin resistance. HA-NPs inhibit not only the receptor-mediated internalization of low-molecular-weight (LMW) free HA but also LMW free HA-induced pro-inflammatory gene expression in mouse primary bone marrow-derived macrophages (BMDMs) isolated from wild type mice. Following systemic administration of C57/6-labeled HA-NPs, in vivo biodistribution assay and immunofluorescent staining indicate the distribution of HA-NPs and their co-localization with CD44 in adipose tissues including epidydimal white adipose tissue (eWAT). However, these effects are largely reduced or rarely observed in BMDMs isolated from CD44-deficient mice. In addition, diet-induced obese (DIO) mice fed a high-fat diet (HFD) show elevated CD44 expression and HA-NP accumulation in eWAT compared to mice on standard diet. Treatment with HA-NPs in HFD-fed DIO mice suppresses macrophage infiltration into adipose tissue and adipose tissue inflammation, leading to improved insulin sensitivity and glycemic control. It is revealed that HA-NP itself can be a therapeutic agent for the treatment of type 2 diabetes.

Supported By: Japan Ade-Supported Research

2004-P

Zinc Alpha2 Glycoprotein Promotes Browning in Adipocytes

XIN-HUA XIANG, XIAN-YAN QI, YA-DI WANG, CAN-XIN XU, JING-HUA LIU, Heng-yang, China, Shanghai, MO.

Recent studies have highlighted recruiting and activating beige adipocytes in WAT (so-called “browning”) would be an attractive anti-obesity strategy. Zinc alpha2 glycoprotein (ZAG) as an important fat-adipokine, is reported to ameliorate glycolipid metabolism and lose body weight in obese mice. However whether the body reducing effect mediated by browning programme remains unclear. Here, we show that overexpression of ZAG in 3T3-L1 adipocytes enhanced expression of brown fat-specific markers (UCP1, PRDM16 and CIDEA), mitochondrial biogenesis genes (PGC-1α, NRF-1/2 and mtTFA) and the key lipid metabolism lipases (ATGL, HSL, CPT-1A and p-acyl-CoA carboxylase). Additionally, those effects were dramatically abolished by H89/SB203580, revealing ZAG-induced browning depend on PKA and p38 MAPK signaling. Overall, our findings suggest that ZAG is a candidate therapeutic agent against obesity via induction of brown fat-like phenotype in white adipocytes.

Supported By: National Natural Science Foundation of China (81270252, 8107066/7), Major Scientific Research Projects of Hunan Health and Family Planning Commission (A2017011)

2005-P

The SDf1-CXCR4 Signals Regulate Adipose Tissue Expansion by Modulating Angiogenesis in Diet-Induced Obesity in Mice

TSUTOMU WADA, ERI WATANABE, YURI KOTERA, YASUHIRO ONOGI, HIROSHI TSUNEKI, TOSHIYASU SASADA, Iwayama, Japan

Adipose tissue (AT) expands with angiogenesis in obesity. Mature vessels in the epididymal white adipose tissue (eWAT) are tightly wrapped with pericytes (PCs), which attenuates endothelial (ECs) proliferation. We found that obesity-associated increase of PDGF-B promoted detachment of PCs from nature vessels; thereby vessels were prone to neoangiogenesis. In this study, we aimed to clarify the role of stromal cell derived factor 1 (SDF1), another proangiogenic factor in the AT development in obesity. In the whole-mount immunofluorescence study of organ cultured eWAT, treatment with PDGF-B or SDF1 for 24 h significantly promoted detachment of PCs from vessels. The effect of SDF1 on PCs was reproduced by treatment with ATI2341, a potent CXCR4 agonist, but not by VUX11207, a CXCR7 agonist. Interestingly, PCs were well associated with vessels when tissue was treated with both PDGF-B and SDF1. In addition, the association was declined by preincubation with AMD3100, a CXCR4 antagonist or when AT was derived from Pdgfrb knockout mice. To further explore the in vivo effect of SDF1 in AT during obesity, we administrated Angliptin (Anal), a DPP-4 inhibitor to C57BL/6J mice fed chow or HFD for 12 weeks, since SDF1 is a known substrate for DPP-4. The protein amount of SDF1 was significantly elevated in the eWAT of Anal-treated mice. Importantly, HFD-induced adipose tissue biology (WHRadjBMI). However, the exact function of this gene in adipose tissue development and obesity remains largely uncharacterized.

In conclusion, since D-SPA were found to express UCP1 and PLF, which were detected in beige cells, but not VAT, SPA were considered to be a progenitor of beige cells. There might be two lineages of cells in adipose tissue; adipose progenitor cells in SVC and VAT (PLF-); and SPA and beige cells (PLF+). The combination of pigilastone and CL316423 produced an additive effect of inducing browning in SPA.

ADA-Supported Research

Moderated Poster Discussion

Integrated Physiology/Obesity

POSTERS

A527
expansion was significantly attenuated with reduced vascular density and PCs detachment in the eWAT by Ana. To clarify the mechanism by which PCs attach even under HFD-fed condition by coexistence of SD1 and PDGF-B, we isolated ECs, PCs, and macrophages (Mφ) from eWAT of mice. Expression of PDGF-B was increased in Mφ and decreased in ECs by HFD, whereas these changes were attenuated and the gradient of PDGF concentration between PCs and ECs was blunted in Ana-treated eWAT. These findings suggest that both PDGF-B and SD1 coordinate to regulate PCs detachments and adipose tissue expansion with obesity in mice.

Supported By: Japan Society for the Promotion of Science; Sanwa Kagaku Kenkyusho

2006-P

Discover and Track Obesity Relevant Research Resources Using dkNET (NIDDK Information Network)
KO-WEI LIN, ANITA BANDROWSKI, JAMES GO, BRAHIM BURAK OZYURT, TOM GILLESPE, JEFFREY S. GRETHE, MARYANN E. MARTONE, La Jolla CA

The NIDDK Information Network (dknet.org) is a portal for basic and clinical investigators that makes it easier to discover, obtain, and reuse scientific research resources. Here we demonstrate how dkNET can connect researchers to resources for obesity research. A search for “obesity” returns 264,498 results (Table 1), including physical resources (i.e., antibodies, cell lines, model organisms), digital resources, data, models, and knowledge bases. dkNET facilitates discovery not only within well known databases like GEO, Mouse Phenome Database, or model organism databases such as MMRRC, but also many unique but less well known databases, such as Animal Quantitative Trait Loci or Aging Gene/Interventions databases.

dkNET provides some basic analytic tools, e.g., word clouds, category graphs, to aid exploration. dkNET provides detailed information on how resources are used through Research Resource Identifier (RRID), a unique ID allowing dkNET to aggregate and provide information, e.g., about known problems with antibodies or cell lines. To assist researchers in complying with NIH guidelines on rigor and transparency, dkNET provides a tool to suggest authentication plans for key research resources. dkNET also provides reports to track resource utilization. These new services aim to not only enhance transparency of research but also ensure that resource creators are appropriately credited.

Table 1 Number of search returns in different categories using “obesity” or “diabetes” as keywords (Jan. 6, 2016). A search for “obesity” returns 264,496 results from 88 data sources, and a search for “diabetes” returns 1,225,794 results from 114 sources.

<table>
<thead>
<tr>
<th>Category</th>
<th>Keyword 1: Obesity</th>
<th>Keyword 2: Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Resources: Antibody</td>
<td>45</td>
<td>42</td>
</tr>
<tr>
<td>Physical Resources: Cell Line</td>
<td>447</td>
<td>10,321</td>
</tr>
<tr>
<td>Physical Resources: Model Organism</td>
<td>416</td>
<td>717</td>
</tr>
<tr>
<td>Digital Resources</td>
<td>169</td>
<td>473</td>
</tr>
<tr>
<td>Data or Model</td>
<td>1,976</td>
<td>3,164</td>
</tr>
<tr>
<td>Funding</td>
<td>41,719</td>
<td>241,390</td>
</tr>
<tr>
<td>Information (gene or protein structure, interaction, phenotype, knowledge bases etc.)</td>
<td>219,539</td>
<td>969,085</td>
</tr>
<tr>
<td>Other</td>
<td>176</td>
<td>546</td>
</tr>
</tbody>
</table>

Total Number of Sources | 88 | 114 |
Total Number of Results | 264,498 | 1,225,794 |

Supported By: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases (U24DK09777)

2007-P

LRP1 Regulates Adiposity by Controlling Energy Balance in MC4R Neurons
MIN-CHOE KANG, JIA, S. SEO, HYUNSOO CHO, HYUNNA LEE, YOUNG-BUM KIM, Boston, MA; Ansan, Republic of Korea

Hypothalamic low-density lipoprotein receptor-related protein 1 (LRP1), a member of LDL receptor family, plays a pivotal role in the regulation of food intake and body-weight homeostasis. However, the role of LRP1 in MC4R-expressing neurons remains unknown. This study was to determine whether deleting LRP1 from MC4R-expressing neurons affects adiposity and energy balance in mice. Here we show that MC4R neuron-specific LRP1 deletion results in decreased body weight in mice fed a normal chow diet (control 30.4±0.6g vs. MC4R-LRP1 deficient mice 27.2±0.5g, p<0.05). Consistent with this, MRI analysis indicated that fat mass in MC4R-LRP1 deficient mice significantly decreased by ~64% without changes in lean mass, compared with control mice. This occurred despite the fact that MC4R-LRP1 deficient mice are hyperphagic (control 3.99±0.17g vs. MC4R-LRP1 deficient mice 4.71±0.18g, p<0.05). In addition, MTII’s ability to suppress food intake was impaired in MC4R-LRP1 deficient mice. These effects are mainly due to increased energy metabolism, as evidenced by the fact that oxygen consumption for 24 hours increased in MC4R-LRP1 deficient mice compared with control mice (control mice 602±287 ml/kg/hour vs. MC4R-LRP1 deficient mice 712±1947 ml/kg/hour, p<0.01), along with exhibiting insulin sensitiv...

Supported By: ADA-Supported Research

2009-P

Empagliflozin and Linagliptin Administered in Combination or as Serial Add-On Therapy Decreases Macrovascular and Microvascular Stiffening and Microalbuminuria in a Mouse Model of Diabetic Nephropathy
ANNAYYA R. AROR, JAYAD HABIBI, GUANGHONG JIA, THOMAS KLEIN, ERIC MAYOUL, VINCENT DEMARCO, Columbia, MO, Biberach, Germany, Ingelheim, Germany, Rocheport, MO

Diabetic individuals are at increased risk for progression of proteinuria and renal fibrosis. There is an urgent need for more effective therapeutic strategies since conventional anti-hyperglycemic therapies may not sufficiently reduce renal injury. Combinations of newer anti-hyperglycemia therapies such as, DPP-4 and SGLT2 inhibitors, which improve glycaemia by differing mechanisms and exhibit cardiovascular and renal protections may show promise in this regard. We tested the hypothesis that targeting SGLT2 and DPP-4 improves aortic and renal vascular stiffening as well as suppression of renal tissue injury. Eleven week old femoral arteries were fed a mouse chow or WD containing excess fat (46%) and fructose (17.5%) for 16 weeks. Insulin sensitivity and vascular activity were determined by intraperitoneal glucose tolerance test and wire myograph system. ECMR KO mice prevented WD-impaired systemic insulin sensitivity and improved the aortic vasodilation responses to acetylcholine (10⁻⁴, 10⁻³ mol/L) and insulin (0.1-300 ng/ml), which were impaired by WD. The impairment of insulin sensitivity and vascular function was associated with abnormal expression of noncoding RNA including miRNA-7, -23, -34, -92, -429, -488, -466 as well as long noncoding RNA-kis2, -Mirt1, -Nron, -Dox2 examined by RNA sequencing, which are associated endothelial inflammation and vascular remodeling. In vitro cultured ECs, aldosterone (10⁻⁷ mol/L) also increased ECs glucose release and miR-103 expression. Furthermore, application of a miR-103 inhibitor to ECs in vitro attenuated aldosterone-induced downregulation of serine (Ser)1177 activation of endothelial nitric oxide synthase and upregulation of intercellular adhesion molecule 1. These findings suggest that increased ECMR signaling and associated abnormal expression and release of noncoding RNA and exosome play a key role in obesity-induced vascular stiffness and insulin resistance.

Supported By: American Diabetes Association (1-17-BS-201 to G.J.)
Evidence of CB1-Receptor Antagonism in Fat-Fed Dogs Promoting Beiging of Adipose Tissue Mainly via Activation of Sarco/Endoplasmic Reticulum Ca2+ ATPase 2b and Ryanoide Receptor 2

REBECCA L. PASZKIEWICZ, RICHARD N. BERGMAN, JOYCE M. RICHEY, MALINI SANDOVAL, Ann Arbor
CHELSEA HUTCH, DARIA STELMAK, KANAKADURGA SINGER, DARLEEN A. KOLZ, Los Angeles
VARID KABIR, Bethesda

We have previously demonstrated that 16 weeks following exposure to a high fat diet (HFD), dogs treated with the CB1-receptor antagonist Rimonabant (RMI) upregulated β3-adrenergic receptors, FGIC1α, Prdm1b, and slight increase of UCPI in the subcutaneous (SC) and visceral (VIS) depots when compared to control treated dogs. These data suggest an improvement in metabolic flux of adipose tissue consistent with beiging. The mechanism(s) by which RIM promotes adipose tissue beiging is unknown. We hypothesize that the beiging effect might be induced via UCP1-independent thermogenic mechanisms through upregulation of sarco/endoplasmic reticulum Ca2+-ATPase 2b (SERCA2b) and ryanoide receptor 2 (RYR2). To explore the mechanism by which RIM enhances adipose tissue function, dogs were fed a HFD (52% fat) for 6 weeks followed by a continued 16 weeks of feeding with either HFD + placebo (PL) (n=9) or HFD + RIM (1.25 mg/kg per day; n=11). Biopsies from SC and VIS depots were obtained for gene expression: before HFD (pre-fat) and 16 weeks of HFD +/- RIM. RIM increased SERCA2b expression in the SC depot by 8-fold (P<0.05) and in the VIS depot by 2-fold (P<0.05) compared to the PL+HFD groups. Also, RIM increased RyR2 expression in the SC (P<0.005) and 4-fold in the VIS depot (P<0.05). Our data suggest that a potential mechanism by which CB1-receptor antagonism increases beiging of adipose tissues may be through upregulation of the key genes involved in an UCP1-independent pathway. Importantly, for the first time we are beginning to identify mechanisms by which CB1-receptor antagonism enhances adipose tissue function and improves energy homeostasis in the presence of a HFD.

Supported By: National Institutes of Health

2011-P

Gender-Dependent EPO Action in Adipose Tissue

JEELYOUNG LEE, CONSTANCE T. NOGUCHI, Bethesda MD

Erythropoietin (EPO) is a glycoprotein that stimulates the production of red blood cells. Recent studies have shown the nonerythroid effect of EPO involved in metabolic regulation. EPO treatment attenuates body weight gain in male mice on normal chow, high fat diet induced obese mice and obesity modulation of body weight is concomitant with reduction in fat mass. EPO improved glycemic control in both male and female obese mouse models. However, the metabolic response to EPO to reduce weight gain primarily via reduced fat mass appears to be gender specific. Although EPO reduced weight gain in 6 month old female mice on high fat diet, regulation of body weight was not observed in young female mice on high fat diet. In contrast, young ovariectomized female mice on high fat diet showed EPO reduction in weight gain. This sex-specific reduction in weight gain is associated with female hormones as the decreased weight gain with EPO treatment in ovariectomized female mice on high fat diet is abrogated with estrogen supplementation. To determine specific in vivo consequences of potential gender differential response of white adipose tissue with EPO treatment, we examined signal transduction in diet induced obese mice following acute EPO treatment. Analysing white adipose tissue harvested at 0, 30 min and 60 min following single dose administration of EPO (3000 U/kg), we found that EPO activated Erk signaling in white adipose tissue of male mice. In contrast, there was no evidence of acute Erk response in white adipose tissue of female mice following EPO treatment. Erk is known for its involvement in adipocyte differentiation, adiposity, and high-fat diet induced obesity. These data suggest that estrogens is a key modifier in the metabolic response to EPO, in part via EPO regulation of Erk signaling with gender specificity. Together, these results elucidate a potential mechanism for cross talk between EPO and estrogen, and provide a novel insight about gender specific EPO action to control adipose tissue development.

Supported By: National Institutes of Health

2012-P

Diet-Dependent Sex Differences in the Response to Bariatric Surgery

CHITRA DE HUTCHE, DARIO STELMAK, KANAKADURGA SINGER, DARLEEN A. SANDOVAL, Ann Arbor MI

Despite the well-known efficacy of bariatric surgery in reducing body mass and improving metabolic outcomes, the mechanisms underlying these dramatic effects are not fully understood. Nearly 80% of patients that receive bariatric surgery are women, yet mechanistic pre-clinical studies have focused exclusively on males. Premenopausal women have a reduced risk for obesity-associated co-morbidities and enhanced lipid metabolism. Although both sexes lose weight and benefit metabolically after bariatric surgery, clear physiological sex differences in metabolism suggest the mechanism/pathway to those outcomes are dependent upon sex and hormone status. The goal of this study was to determine the impact of diet- and surgery-induced weight loss on sex differences in glucose regulation and hepatic lipid metabolism. Male and female mice were fed a 60% high-fat (HF) diet 12 weeks before undergoing either vertical sleeve gastrectomy (VSG) or sham surgery. After surgery, mice either remained on a HF diet or were switched to a standard chow diet. Both males and females decreased fat-mass after VSG, yet males showed further body mass loss on a chow diet. Both sexes improved fasting glucose and oral glucose tolerance on a HF diet after VSG, while only males showed further benefit from surgery and chow diet. Despite the continued HF diet feeding, male but not female mice show significant improvements in hepatic triglyceride levels after VSG relative to their sham surgery counterparts. However, when mice were switched to a low-calorie chow diet both males and females reduced hepatic triglycerides after VSG. Furthermore, removing female gonadal hormones, via ovariectomy, did not impact hepatic triglyceride levels after VSG. Overall, these data suggest that the impact of surgery on hepatic triglycerides is diet-dependent in females and support the hypothesis that males and females achieve similar metabolic outcome, at least within the liver, via distinct mechanisms.

Supported By: National Institutes of Health (T32DK010355)

2013-P

Impairment of M2a-Subtype Macrophage Activation by I-4-lrs2 Pathway in Obesity

TETSUYA KUBOTA, MARIKO INOUE, NAOTO KUBOTA,ISEKI TAKAMOTO, KOHJIRU Ueki, TOSHIMASA YAMAMUCHI, TAKASHI KADOWAKI, Tokyo, Japan

Introduction: M2a-subtype macrophage activation is known to be impaired in obesity, although the underlying mechanisms remain poorly understood. Methods: We found that the phosphorylation levels of Irs2 by I-4-lrs2 were significantly reduced along with decreased Irs2 expression in macrophages of high-fat (HF) diet-fed mice. To investigate the role of Irs2 in the macrophages, we then generated myeloid cell-specific Irs2-deficient (Mirs2KO) mice.

Results: HF diet-fed Mirs2KO mice showed impairment of I-4-lrs2 macrophage activation, resulting in insulin resistance. Expressions of the maker genes for M2a-subtype macrophages were downregulated by stabilization of the FoxO1/HDAC3/NcoR1 repressor complex via impairment of the I-4-lrs2 pathway. Furthermore, Irs2 expression was significantly suppressed in insulin treatment in macrophages, suggesting that chronic hyperinsulinemia downregulates macrophage Irs2 expression via insulin receptor (IR). Indeed, in myeloid cell-specific IR-deficient mice, the I-4-lrs2 pathway was preserved in the macrophages due to the lack of IR-mediated downregulation of Irs2, resulting in a reduced degree of inflammation and insulin resistance.

Conclusion: These data suggest that in obesity, downregulation of macrophage Irs2 is induced by hyperinsulinemia, resulting in impaired I-4-lrs2 subtype macrophage activation, and insulin resistance.

2014-P

Siah2 in Adipocytes Promotes M2-Like Macrophage Activation in Adipose Tissue

GAIL E KLROV, JESSICA L TAYLOR, THANH DANG, YONGMEI YU, ELIZABETH FLOYD, Baton Rouge, LA

Obesity is associated with chronic, low-grade adipose tissue inflammation that is linked to glucose intolerance and insulin resistance. Although enzymes of the ubiquitin-proteasome system are known to regulate signaling in classical inflammation, involvement of the ubiquitin-proteasome system in obesity-induced metabolic inflammation is relatively unexplored. We previously found that the ubiquitin ligase mammalian homolog of seven-in-absentia (Siah2) alters peroxisome proliferator-activated receptor γ (PPARγ)
protein levels and selectively regulates PPARα activity. Using a mouse model of global Siah2 deletion (Siah2KO), we observed that Siah2KO mice become obese on a high fat diet (HFD), but remain glucose tolerant and insulin sensitive. This corresponds to reduced expression of pro-inflammatory markers, substantially fewer crown-like structures and less fibrosis in adipose tissue although the adipocytes are enlarged. To determine if expression in adipocytes accounts for the Siah2KO phenotype, we created an adipocyte specific Siah2KO model (Siah2AdKO). Although HFD-induced obesity is attenuated in Siah2AdKO mice, the mice become glucose intolerant and insulin resistant. The visceral adipose tissue is infiltrated by M1-like macrophages, corresponding to increased crown-like structures and fibrosis while M2-like macrophages are reduced. PPARα activity is selectively regulated, but PPARα protein levels are unchanged in the Siah2AdKO mice. The levels of pro-inflammatory markers such as IL-6 are increased, but as in the global Siah2KO model, TNFα, SAA3 and PAI-1 expression is decreased. Thus, our data indicates Siah2 in adipocytes influences polarization of macrophages in adipose tissue independent of regulating PPARα protein levels. Moreover, Siah2 in adipocytes mediates expression of a subset of pro-inflammatory adipokines, but surprisingly, these factors do not appear to drive adipose tissue inflammation in this model of obesity.

Supported By: National Institutes of Health (R01DK096925)

Dipeptidyl Peptidase-4 Inhibition with Linagliptin Promotes Angiogenesis/Vasculogenesis in the Hearts of Female Diabetic db/db Mice

RYAN TOEBUSCH, ANNAYA R. ARDOE, JAVAD HABIBI, THOMAS KLEIN, LAKSHMI PULAKAT, VINCENT DEMARCO, Columbia, MO; Biberach, Germany, Rocheport, MO

We previously reported that the DPP-4 inhibitor linagliptin (LINA) prevents diastolic dysfunction and myocardial fibrosis in a mouse model of diet-induced obesity, a pre-clinical model of prediabetes. LINA suppressed WD-induced pro-inflammatory mediators, such as TGRAFIP2 and downstream signaling intermediates, NF-κB, AP-1 and p38-MAPK in the heart. Herein, we extend that study by testing whether LINA slows progression of diastolic dysfunction in diabetic db/db mice, and improves the underlying maladaptive immune/inflammatory response. To accomplish this, we fed db/db mice normal mouse chow with or without linagliptin (38 mg/kg chow). After performing echocardiography on mice treated or not for 10 weeks, we analyzed expression of 200 cytokines in myocardial extracts and performed Ingenuity Pathway Analysis (IPA) in an effort to determine what signaling pathways are predicted to be differentially activated in the heart. Mouse treated with linagliptin had improved diastolic function indicated by lower LV filling pressure compared to untreated mice (E/E'; 35 vs. 50; p<0.05). IPA predicted that LINA activates pathways contributing to cardiovascular development of the vasculature (32 molecules, Activation z-score = 3.7), angiogenesis (31 molecules, Activation z-score = 3.7) and vasculogenesis (27 molecules, Activation z-score = 3.7). Cardiomyocyte size (i.e., cross-sectional area) was reduced by 23% (553±30 vs. 411±18 μm²; p<0.05) and myocardial capillary density was two-fold higher with LINA treatment compared to untreated mice (p<0.05). In addition, the proteome analysis showed a significant decrease in TNF-α related apoptosis inducing ligand, a cytokine that induces endothelial nitric oxide, in untreated mice, however, this deficiency was prevented by LINA. These data suggest that linagliptin exerts a beneficial immune/inflammatory response in the diabetic heart that confers myocardial vasculoprotection.

Supported By: Boehringer Ingelheim

Liver-Specific Reactivation of MC3R Partially Reverses the Obesity of MC3R Deficiency

NGAHI J. LEVI, JIHYUN JUN, TUSHAR P. PATEL, ANDREW J. UHLMAN, ROBIN ROBERSON, JACOB A. YANOFSKI, BOSTON, MA

The Melanocortin 3 Receptor (MC3R) regulates appetite, food intake, and energy expenditure in humans and mice. MC3R is primarily expressed in the hypothalamus and other CNS regions but is also present in peripheral tissues including the liver. Total body knockouts of MC3R have a distinct obese phenotype of increased fat mass with decreased lean mass. However, when MC3R is reactivated only in the brain of mice that are globally MC3R deficient, the obese phenotype is not completely reversed compared to wild type mice, suggesting peripheral MC3R may also regulate energy homeostasis. To begin to examine the role of peripheral MC3R in energy balance, we investigated the extent to which liver specific reactivation of MC3R reversed the obese phenotype seen in the global knockout. We generated a liver specific MC3R recovery model by crossing a floxed-transcription blocker MC3R (MC3R/+) mouse line with mice expressing albumin-Cre recombinase (Alb-Cre+/-); both strains were in a C57BL/6J (BL/6) background. We measured the body weight and body composition (using dual energy X-ray absorptiometry) of 10-12-week-old MC3R+/−, MC3R−/− + Alb-Cre +/-, and MC3R−/− + Alb-Cre −/− and BL/6 mice. We found amongst female mice that expression of Alb-Cre (reactivating only hepatic MC3R) was sufficient to partially reverse the increased percentage fat mass of MC3R−/− mice (n=15, 21.15 ± 4.78%; MC3R+/− + Alb-Cre +/−; n=21, 22.12 ± 3.13%; MC3R−/− + Alb-Cre −/−: n=3, 17.83 ± 4.04%; BL/6: n=17, 15.72 ± 3.18%; p < 0.0001). A similar pattern of partial recovery was also observed for fat grams (p=0.0009), % lean mass (p=0.0003), and lean grams (p=0.002), with no differences in body weight amongst genotypes (p=0.812). Data for male mice were insufficient to perform analyses at this time. We conclude hepatic MC3R is an important regulator of energy homeostasis and body composition. The potential roles for MC3R in other tissues where it is expressed remain to be determined.

Supported By: Boehringer Ingelheim

Mice Lacking Both Cannabinoid-1 and Cannabinoid-2 Receptors Are Resistant to Diet-Induced Obesity

OMAYMA ALSHAARAWY, EMILY KURJAN, NGUYEN TRUONG, LAWRENCE K. OLSON, East Lansing, MI

Exogenous cannabinoids are a group of related compounds derived from the Cannabis plant, commonly known as marijuana. The discovery of cannabinoid receptors (CB1R and CB2R) has provided a platform for investigating the health effects of cannabinoids. The CB1R is predominantly expressed in the central nervous system, whereas CB2R is primarily expressed in the immune system. Mounting evidence has shown that activation of CB1R is associated with increased food intake and obesity, whereas activation of CB2 is associated with decreased levels of cytokines associated with insulin resistance and type 2 diabetes (T2D). Epidemiological studies, however, have shown a decreased prevalence of obesity and T2D among cannabis users. Although the exact mechanism of this effect is not fully understood, one possible explanation is that mice lacking both cannabinoid receptors are resistant to diet-induced obesity.
users. Here we use high-fat diet (HFD), 45% of calories from fat vs. control LFD with 10% of calories from fat) to study the metabolic changes in male mice lacking receptors of the cannabinoid system (CB-DKO) when compared to wild type (WT) C57BL/6 mice. Eight-week old CB-DKO mice displayed lower body fat percent and higher percent of lean mass tissue when compared to WT mice. After 12 weeks, mice gained an average of 22 g on HFD compared to 9 g on LFD. CB-DKO mice did not respond to HFD, gaining an average of 5 g on both HFD and LFD. This corresponded to a 5% increase in body fat in CB-DKO mice compared to 18% increase in WT mice. Glucose tolerance test indicated increased insulin sensitivity in CB-DKO mice. Automated measurements revealed no significant differences in food intake or locomotion between CB-DKO and WT mice, whereas CB-DKO mice displayed higher indirect calorimetry parameters including VO2, respiratory exchange ratio, and energy expenditure. Gene expression analysis confirmed an upregulation of thermogenic genes (UCP1, CIDEA, and COX8B), suggesting browning of white adipose tissue in CB-DKO mice. These findings highlight the role of the cannabinoid system in metabolic control of adipose tissues and their potential role for insulin resistance and T2D risk.

Supported By: National Institutes of Health; National Center for Complementary and Integrative Health (K08AT009156)

2019-P

Compound C Protects Mice from Diet-Induced Obesity and Hepatosteatosis

FANG WANG, WENJUN YANG, RONG XIAO, JING JING YUAN, YUXING LIU, KE ZHENG, ZHAOQI WANG, CHANGSHA KEZHU CHEN, ZHANGXI MO, Changsha

Introduction and Aims: Obesity and its resulting metabolic disturbances are major health threats and are the main cause of nonalcoholic fatty liver disease (NAFLD). Compound C has been demonstrated to be not only an inhibitor of AMPK, but also has some actions independent of AMPK inhibition. In our previous studies, we unexpectedly found compound C is an anti-inflammatory and anti-NLRP3 inflammasome activator in vitro. The aim of this study was to investigate the effects of compound C on a mouse model of high-fat diet (HFD) (60 kcal% fat)-induced obesity and hepatosteatosis in vivo.

Methods: C57BL/6 mice were fed with either a standard or a HFD for 14 weeks. These mice were divided into three groups (Normal Chow, HFD + Vehicle, and HFD + compound C (6 mg/kg i.p., once a day)) and treated for an additional 4 weeks. All animals were weighed weekly and food intakes measured twice weekly. Liver histology as well as pro-inflammatory gene expression in liver and white adipose tissue (WAT) were examined.

Results: There was a significant reduction in body-weight gain and daily food intake in compound C-treated group compared with HFD group (P < 0.05). Glucose tolerance test and insulin tolerance test showed that compound C increased glucose metabolism and alleviated insulin resistance compared with the HFD group. Histology analysis showed a significant reduction of hepatic steatosis and ballooning by compound C. To further characterize the activity of compound C, quantitative RT-PCR analysis of pro-inflammatory markers were performed, demonstrating that compound C significantly reduced IL-1β, IL-8, IL-6, and TNF-α gene expression in the liver as well as in the WAT (P < 0.01). Moreover, NLRP3 inflammasome which plays an important role in obesity and NAFLD was significantly decreased by compound C using western blot analysis.

Conclusions: Taken together, these results suggest that compound C offers the potential as a novel therapy for obesity and NAFLD, probably by impairing NLRP3 inflammasome activation and the related inflammation.

Supported By: National Natural Science Foundation of China (81400831), Third Xiangya Hospital of Central South University (201718)

A531

2020-P

Ldb1 Transcriptional Coregulator Is Required for Brown Adipose Development and Function

JESSICA KEPPLE, YANPING LIU, TEAYOUN KIM, GLENN C. ROWE, KIRK M. HABEGGER, CHAD S. HUNTER, BIRMINGHAM, AL

Brown adipose tissue (BAT) is critical for thermogenesis and glucose homeostasis. BAT utilizes fatty acids and glucose for heat production via mitochondrial uncoupling, and is thus an attractive therapeutic target for combating obesity. Exploiting the energy uncoupling capacity of this tissue requires a greater understanding of underlying BAT transcriptional mechanisms. We recently reported on a transcriptional co-regulator, LIM domain binding protein 1 (Ldb1), which appears to have novel roles in BAT biology. Ldb1 acts as a dimerized scaffold allowing for the assembly of transcriptional complexes and is important for the development and function of many tissues, including the brain and pancreatic islets. However, direct roles for BAT-expressed Ldb1 have not been elucidated. We set out to test the hypothesis that Ldb1 directly impacts BAT development and function. We developed a mouse model in which Ldb1 was deleted in thermogenic adipocytes using an Uncoupling protein 1 (Ucp1)-driven Cre recombination, termed Ldb1ΔMNT. These knockout mice had reductions in BAT-selective mRNAs, including Ucp1 and Elov12, a result similarly observed in Xb beige cell lines lacking Ldb1. Ldb1ΔMNT mice were unable to defend body temperature during a cold challenge, suggesting thermogenic defects. We also observed glucose intolerance in Ldb1ΔMNT mice via intraperitoneal glucose challenge. Ldb1 deletion in preadipocytes resulted in reduced Ucp1 expression upon induction to mature adipocytes. These data suggest a direct role for Ldb1 in maintaining thermogenic and metabolic function in BAT, as well as a developmental role in preadipocytes. Additional metabolic and transcriptional profiling of the Ldb1ΔMNT model will interrogate the mechanisms underlying Ldb1 control of BAT function, potentially leading to novel obesity and diabetes therapeutic targets.

Supported By: American Diabetes Association (16-JDF-044 to C.S.H), National Institutes of Health (732GM109780)

2021-P

Adipocyte Lipolysis Triggers CD11c-ATM Inflammation in Lean Females and Obese Males and Females

MITA VARGHESE, SIMIN ABRISHAMI, KANAKADURGA SINGERT, ANR ADOROT, MI

Men and post-menopausal women are at greater risk for cardiovascular diseases and diabetes than younger women. In obese rodent models, males exhibit profound adipose tissue macrophage (ATM) accumulation in gonadal white adipose tissue (GWAT), linked to insulin resistance, while females are protected even with enhanced adiposity. We hypothesize that these inflammatory differences may be a result of altered lipolysis responses and that females would have enhanced ATM accumulation when lipolysis is induced. Lipolysis was stimulated with a beta3 adrenergic receptor (ARDB3) agonist Cl-316,243 in male and female mice fed 16 weeks of 45% high fat diet (HFD). GWAT leukocytes were isolated after 18 h and evaluated by flow cytometry. Lipogenic, lipolytic, oxidative and inflammatory gene expression along with immunofluorescence were performed. ARDB3 activation did not alter adipose tissue weights, but significantly reduced liver weights in obese females. Obese CL treated female mice showed elevated serum free fatty acid (FFA) and triglyceride (TG) levels compared to levels induced in males. Lipid overload impaired TG storage and utilization genes - Lpl, Fasn, Acsl1, Hsl, and Glut4 expression in obese females. Lipolysis promoted appearance of crown like structures (CLS) in males and females but only induced β3 proinflammatory cytokine and Mcp1 chemokine expression in obese female GWAT. Activated lipolysis triggered CD11c+ ATM accumulation in lean females but in both obese male and female GWAT. Obese males showed a marked reduction in GWAT dendritic cells (DC) but a significant reduction in both GWAT and inguinal WAT DCs of obese females. While obese females are resistant to inflammation, this study shows that induced lipolysis elevates FFA levels, alters lipid metabolism and increased CD11c+ ATMs and CLSs in obese females. Elucidating the link between lipolysis and inflammation can better explain sex differences in overall metabolic health leading to targeted treatment strategies.

Supported By: University of Michigan

Identification of Novel Transcriptional Regulators of Uncoupling Protein 1 Using a Modified CRISPR-Cas9 Methodology

JUSTIN DARCY, CHIH-HAO WANG, MORTEN LUNDH, FARNAZ SHAMS, MATT LYNES, BRICE EMANUELLI, YU-HIA TSENG, BOSTON, MA, COPENHAGEN, DENMARK

Obesity is an epidemiological dilemma due to its associated comorbidities such as diabetes, cancer, and heart disease. Because traditional weight loss strategies such as diet and exercise are thus far ineffective at curtailting the growing prevalence of obesity, new therapeutic approaches are being sought after. In this regard, brown adipose tissue (BAT) has garnered attention due to its ability to burn fat as fuel during thermogenesis, which is carried out by the mitochondrial uncoupling protein 1 (UCP1). Since UCP1 is mainly regulated at the level of transcription, our laboratory sought to identify novel transcriptional regulators of UCP1 using a modified CRISPR-Cas9 methodology termed engineered DNA-binding molecule-mediated chromatin immunoprecipitation (enChIP) (Fuji and Fujita, 2015). enChIP takes advantage of dCas9, which lacks endonuclease activity while maintaining functional DNA binding activity, fused to a 3xFLAG tag that can be used for immunoprecipitation. For our study, we delivered five guide RNAs (gRNAs) targeting the Ucp1 promoter region in a mouse-derived mature brown adipocyte line that had been modified to endogenously express the dCas9-3xFLAG fusion protein. Following treatment with either vehicle or C316,243, we immuno-
High Iron Feeding Modulates Glucose Metabolism in Duodenal-Jejunal Bypass Surgery but Not in Vertical Sleeve Gastrectomy in Mice

JINGJING NIU, JONATHAN D. DOUGROES II, JONATHAN CAMPBELL, MEGAN CAPOZZI, SARAH M. GRAY, FELIPE LORENZO, DAVID D’ALESSIO, DON MCCLAIN, JENNY TONG, Durham, NC, Winston-Salem, NC

High dietary iron intake is associated with impaired islet-cell function and increased risk of type 2 diabetes mellitus (T2DM) while iron chelation leads to improved glucose tolerance. Bariatric surgery has multiple metabolic benefits but iron-deficiency anemia is a common occurrence following surgery, presumably because of preferential iron absorption in the upper intestine. We hypothesized that a duodenal-jejunal bypass (DJB) procedure that bypasses the proximal small bowel and vertical sleeve gastroectomy (VSG) that eliminate 80% of the stomach without altering the intestine would have differential effects on iron metabolism and glucose homeostasis. C57BL/6J mice were fed either high- (2000 ppm) or low-iron diet (4 ppm) for 18 weeks before DJB (n=6 per diet group), VSG (n=6/7 per diet group) or sham surgery (n=11 per diet group). Intraportal iron, glucose, and insulin, tolerance tests were performed at Day 0, 10 and 20 after surgery. Compared to animals given a low-iron diet, 4 months of high-iron diet significantly impaired glucose tolerance (p<0.05) and decreased insulin and glucagon secretion, but had no effect on body weight or insulin sensitivity prior to surgery. Compared to sham controls neither VSG nor DJB affected glucose or insulin tolerance at day 10 after surgery. However, 20 days after surgery, VSG significantly improved glucose tolerance in both the high- and low-iron diet groups, with increased secretion of islet hormones in vivo test. In contrast, DJB surgery only improved glucose tolerance in the low-iron-fed mice, this response was not present in the high-iron-fed animals. In sum, these findings indicate that high-iron intake modulates the benefits of DJB, but not VSG on glucose metabolism. This is consistent with an important contribution of GI tract handling of dietary iron to the metabolic effect of surgery to improve glucose tolerance.

Supported By: National Institutes of Health

2024-P Diet-Induced Adipose Tissue Inflammation and Hypoxia Are Reversed by GLP-1 Potentially via Improved Microcirculation

FEN XIU, ZONGLAN CHEN, YINGYIN XIAN, HENG R. DENIS, WEN XIU, HUA LIANG, JIANPING WENG, Guangzhou, China, Jining, China

Obesity is considered as an inflammatory disease. A proposed trigger of the inflammation is hypoxia, which occurs when the enlargement of vascular network is not sufficient to support the expanding adipocytes. Exenatide, a GLP-1 receptor agonist, plays an anti-inflammatory role in obesity, however, the etiological factors that alter the number and polarization of adipose-resident macrophages remain poorly characterized. As our previous clinical study has identified microRNA (miR-34a) as one of the most significantly elevated genes in visceral fat of obese patients, we investigated the roles of miR-34a in obesity-related adipose tissue inflammation and metabolic disorders by generated adipose tissue-specific miR-34a knockout (KO) mice. After feeding with high fat diet (HFD), adipose miR-34a KO mice exhibited significant attenuation of HFD-induced glucose tolerance, insulin resistance, hyperlipidemia, steatohepatitis and systemic inflammation compared to HFD-fed wild type (WT) controls. These benefits of miR-34a deficiency were mainly attributed to the reduced number of total macrophages and polarization of adipose macrophages towards the pro-inflammatory M1 phenotype. Mechanistically, we found that miR-34a directly repressed the expression of the transcription factor Klf4, thereby enhancing macrophage polarization to the M1 phenotype. Silencing of Klf4 in the adipose-specific miR-34a KO mice suppressed M2 macrophage polarization. In visceral fat from obese patients, the expression of Klf4 was significantly decreased and negatively correlated with miR-34a level. These data demonstrated that increased miR-34a in adipose tissues exacerbates obesity-induced adipose tissue inflammation by suppressing the expression of Klf4, thereby leading to increased accumulation of pro-inflammatory M1 macrophages.

Supported By: Hong Kong Health and Medical Research Fund (0314516H), Hong Kong Research Grants Council (C7055-14G)

2026-P Characterization of AJ5012 as a Novel Peripheral Cannabinoid 1 Receptor Antagonist in Mouse Models of Obesity

JUNGSEUN KIM, JUHWAN YOON, EUNHA KIM, SUNG-HWA YOON, WOOK KIM, Suwon, Republic of Korea

Obesity-induced adipose tissue inflammation, in which the NLRP3 inflammasome is a pivotal mediator, is implicated in the development of insulin resistance. Cannabinoid 1 receptor (CB1R) antagonists have been shown to improve insulin resistance and the associated metabolic abnormalities, but their therapeutic development was discontinued due to neuropsychiatric side effects. Although growing evidence suggests the role of CB1Rs in proinflammatory signaling, their direct effects on adipose tissue inflammation have not yet been evaluated. Here we report that the peripherally restricted CB1R antagonist AJ5012, which exhibits beneficial metabolic effects comparable with its brain-penetrant parent compound rimonabant, suppresses macrophage infiltration into white adipose tissue, activation of the NLRP3 inflammasome, and production of proinflammatory cytokines in diet-induced obese mice. Moreover, we identified the downstream signaling pathways by which CB1R regulates proinflammatory gene expression. These results suggest that peripheral CB1R blockade improves obesity-induced insulin resistance by suppressing adipose tissue inflammation via the NLRP3 inflammasome.

2025-P miR-34a Aggravates Obesity-Induced Adipose Inflammation and Metabolic Dysfunction via Blocking Polarization of Anti-inflammatory M2 Macrophage

YONG PAN, HANNAH HUI, SR., RLC HOO, TIANSHI FENG, KAREN S. LAM, AIMIN XU, Hong Kong, China

Adipose-tissue resident macrophages are an important contributor to systemic chronic inflammation and cardiometabolic abnormalities associated with obesity. However, the etiological factors that alter the number and polarization of adipose-resident macrophages remain poorly characterized. As we previously identified microRNA (miR-34a) as one of the most significantly elevated genes in visceral fat of obese patients, we investigated the roles of miR-34a in obesity-related adipose tissue inflammation and metabolic disorders by generating adipose tissue-specific miR-34a knockout (KO) mice. After feeding with high fat diet (HFD), adipose miR-34a KO mice exhibited significant attenuation of HFD-induced glucose tolerance, insulin resistance, hyperlipidemia, steatohepatitis and systemic inflammation compared to HFD-fed wild type (WT) controls. These benefits of miR-34a deficiency were mainly attributed to the reduced number of total macrophages and polarization of adipose macrophages towards the pro-inflammatory M1 phenotype. Mechanistically, we found that miR-34a directly repressed the expression of the transcription factor Klf4, thereby enhancing macrophage polarization to the M1 phenotype. Silencing of Klf4 in the adipose-specific miR-34a KO mice suppressed M2 macrophage polarization. In visceral fat from obese patients, the expression of Klf4 was significantly decreased and negatively correlated with miR-34a level. These data demonstrated that increased miR-34a in adipose tissues exacerbates obesity-induced adipose tissue inflammation by suppressing the expression of Klf4, thereby leading to increased accumulation of pro-inflammatory M1 macrophages.

Supported By: Hong Kong Health and Medical Research Fund (0314516H), Hong Kong Research Grants Council (C7055-14G)
deletion of MDM2 induces chronic and unstrained activation of p53, which in turn triggers progressive loss of adipose tissues. Similar to other mouse models with lipodystrophy, mice lacking of adipocyte MDM2 develop hyperglycemia, hyperinsulinemia, hyperlipidemia and massive nonalcoholic fatty liver. Adiponectin-Cre-mediated deletion of MDM2 has no obvious effect on adipogenesis in cell-autonomous manner but induces apoptotic and senescent program in white and brown adipocytes. To ascertain whether the activation of p53 is responsible for the MDM2-null phenotypes, we generated an adipocyte specific MDM2-p53 double knockout mouse model. As expected, lipodystrophy and its associated metabolic disorders are not observed in adipocyte-MDM2-p53 double knockout mice. In addition, transplantation of subcutaneous white adipose tissue largely reverses diabetes, dyslipidemia and nonalcoholic fatty liver in adipocyte-specific MDM2 knockout mice. Together, our data suggest that the balance of MDM2-p53 signaling axis is crucial for proper functions and turnover of adipose tissues.

Supported By: Research Grants Council of Hong Kong (C7055-14G)

2028-P

Weight Loss Outcomes with Species-Specific Dual GLP-1R/GCGR Agonists in Animal Models

RAILF ELVERT, MARTIN BOSSART, BOB ZHANG, AIMO KANNT, MICHAEL WAGNER, TORSTEN HAACK, ANGELA DUDDA, MARTIN LORENZ, STEFANIE KEIL, PHILIP J. LARSEN, RALF ELVERT, ANDREAS EVERS, ANGELA DUDDA, MARTIN LORENZ, STEFANIE KEIL, PHILIP J. LARSEN, Frankfurt, Germany, Kunming, China

Dual agonism of glucagon-like peptide-1 receptor and glucagon receptor (GLP-1 R/GCGR) was shown to reduce body weight. Species-specific dual GLP-1 R/GCGR agonist peptides (SSDA) structurally based on exendin-4 and carrying a fatty acid side-chain for half-life extension, or the selective GLP-1 R agonist liraglutide (lira) were administered to diet-induced obese (DIO) mice twice daily for 32 days, and to DIO and diabetic cynomolgus monkeys once daily for 43 days. Potencies of the SSDA and lira on mouse and monkey GLP-1 receptors were in the single-digit picomolar range. Body weight change was greater with SSDA than with lira in mice (-21.1 ± 2.1% vs. -12.9 ± 1.4%) and monkeys (-8.2 ± 1.2%, p<0.001 vs. -5.1 ± 1.1%, p<0.001; Figure). Indirect calorimetry in mice showed increased total energy expenditure (TEE) in those treated with SSDA, caused not only by increased fat oxidation but also by increased oxidation of carbohydrates. Lira significantly increased (TEE) in those treated with SSDA, caused not only by increased fat oxidation but also by increased oxidation of carbohydrates. Lira significantly increased TEE, but significantly less than SSDA. These data support the mechanistic view that weight loss with SSDA does not result exclusively from reduced food intake but also from increased energy expenditure induced by GCGR activity. In murine and primate models, dual GLP-1 R/GCGR agonism with SSDA led to greater body weight loss than GLP-1 R alone. This represents a novel dual mechanism of action with potential for the treatment of obesity.

Supported By: R&D, Sanofi & ADA-Supported Research & Integrated Physiology/Diabetes

2029-P

Adaptation Process of the Transposed Ileum during Early Postoperative Period after Ileal Transposition

CHANG-HO AHN, TAE JUNG OH, SUN-JOON MOON, SOD HEOON KWAK, KYONG SUO PARK, YOUNG MIN CHO, Seoul, Republic of Korea, Seongnam, Republic of Korea

The intestine undergoes diverse changes to adapt the altered environment after bariatric surgery, which have various implications in the molecular mechanisms of bariatric surgery. Ileal transposition (IT) is an experimental surgery to investigate the role of the distal ileum in bariatric surgeries. To systematically investigate the gut adaptation process in IT, we performed a gene expression profiling of the transposed ileum compared to the ileum in situ at different postoperative time points. Sprague-Dawley rats fed a Chow diet underwent IT or sham surgery. In IT, 10 cm of the distal ileal segment was transposed distal to the Treitz ligament. In sham surgery, the intestine was resected at the same anatomical location and anastomosed in situ. Either 1 or 4 weeks after surgery, total RNA was extracted from the ileal tissue and used for microarray analysis. Principal component analysis showed that the difference between 1 and 4 weeks was the largest. The difference between IT and sham groups were larger at 4 weeks than 1 week. A total of 1792 differentially expressed genes (DEGs) were identified including 659 and 1133 DEGs at 1 and 4 weeks, respectively. Interestingly, only 45 and 24 DEGs were commonly up- or down-regulated at the two time points, remaining 96.1% of DEGs were uniquely regulated at either time points. The network analysis showed that the affected biologic processes were related to structural (cell adhesion and immune responses) and functional (glucose and fatty acid metabolism) adaptations. Up-regulated extracellular proteins and their interacting integrins at 1 week, and cytokines, chemokines and their receptors at 4 weeks were interlinked. In glucose metabolism, up-regulation of GLUT2, HK3 and down-regulation of GPc were suggested enhanced glucose uptake and glycolysis. Collectively, our results suggest that the adaptation process of the transposed ileum dynamically evolve during early postoperative period incorporating structural and functional changes.

Supported By: Korean Ministry of Health and Welfare

2030-P

Genetic Nicotinamide N-Methyltransferase Deficiency Improves Insulin Sensitivity in DIO Mice

SEBASTIAN BRACHS, JAMES POLACK, MARIA BRACHS, KERSTIN JAHN-HOFMANN, RALF ELVERT, ANNA PFENNINGER, FELIX BÄRENZ, DANIEL MÄRGERIE, SR., KNUT MAI, AIMO KANNT, JOACHIM SPRANGER, Berlin, Germany, Frankfurt, Germany

Nicotinamide N-methyltransferase (NNMT) is expressed in most tissues including muscle, adipose tissue, liver and digestive organs. Recent research suggests the involvement of NNMT in the pathogenesis of obesity, insulin resistance and related metabolic disease. Antisense oligonucleotide (ASO) knockdown in high-fat diet (HFD)-fed mice led to reduced weight gain, relative fat mass, plasma insulin levels and improved glucose tolerance. We tested the hypothesis, that genetic NNMT deletion protects mice on HFD and Western diet (WD) against obesity and explored the metabolic effects of NNMT. Using NNMT ASO treatment and a NNMT knockout mouse (NNMT-/-), we investigate the effects of NNMT deletion on energy metabolism, glucose homeostasis and the development of obesity. We also examined data from a human study concerning NNMT expression and 1-methylnicotinamide (MNA) levels regarding weight reduction. In WD-fed mice, NNMT ASO treatment improved acute glucose tolerance, reduced weight gain and fat mass increase and, consequently, lowered plasma insulin levels. NNMT-/- mice exhibited virtually no MNA but threefold higher nicotinamide levels. Whereas NNMT-/- male and female mice on normal chow revealed no metabolic phenotype, NNMT-/- males on HFD showed improved glucose infusion rates, nearly complete insulin-mediated suppression of endogenous glucose production and an enhanced glucose uptake during a hyperinsulinemic-euglycemic clamp. Furthermore, NNMT-/- females on WD showed reduced weight gain, less fat mass and lower insulin levels compared to controls. While NNMT gene expression in human fat biopsies increased over weight loss, corresponding plasma MNA levels significantly declined after weight reduction, suggesting that other mechanisms rather than adipose NNMT expression modulate circulating MNA levels during weight reduction.

In conclusion, we observed an improvement of basal metabolic parameters and insulin sensitivity in NNMT-deficient mouse models.

Supported By: Deutsches Zentrum für Herz-Kreislauf-Forschung, ICMED Consortium; Berlin Institute of Health

ADA-Supported Research, Integrated Physiology/Diabetes, ADA-Supported Research & Integrated Physiology/Diabetes
Low-Dose FGF-21 Administration Decreases Obesity-Induced Hepatic Steatosis, but Has No Effect on Inflammation in Mice

SHALIGRAM SHARMA, SEAN JUNG, EMILY GRAFF, THOMAS W. GETTYS, DESIREE WANDERS, Atlanta, GA; Auburn; AL; Baton Rouge, LA

Pharmacologically, FGF-21 reduces body weight, increases insulin sensitivity, and reduces hepatic lipids in rodents. Preclinical studies suggest that FGF-21 may exert anti-inflammatory effects. We aimed to determine 1.) whether endogenous FGF-21 provides protective effects against high-fat diet (HFD)-induced inflammation, and 2.) whether low-dose administration of FGF-21 reverses HFD-induced inflammation and hepatic steatosis. In experiment #1, wild type (WT) and FGF-21−/− mice (n=8/group) were fed a HFD for 15 weeks. RT-PCR analysis showed that despite weighing slightly less than the WT mice, the FGF-21−/− mice were more susceptible to HFD-induced inflammation of the liver and white adipose tissue (WAT). To test whether administration of FGF-21 provides protection from HFD-induced inflammation, in Experiment #2, 20 male C57BL/6J mice were fed a HFD for 10 weeks. After 10 weeks of HFD feeding, mice were administered vehicle (saline + 0.1% BSA; n=10) or recombinant human FGF-21 (R and D Systems; n=10; 0.3 mg/kg/day) for 14 days via subcutaneous osmotic minipumps. There was no effect on FGF-21 administration on body weight. Histological analysis of WAT showed no effect of FGF-21 on adipocyte size, and no effect on crown-like structure number. Confirming this lack of effect of FGF-21 on inflammation, RT-PCR analyses of liver and WAT showed comparable mRNA expression of inflammatory markers, including Adgre1, Itgam, Itgax, Ccl2, Il1b, and Tnf in the vehicle- and FGF-21 treated groups. Despite having no effect on inflammation, FGF-21 significantly reduced fasting blood glucose levels. Histological evaluation of liver showed that low-dose FGF-21 administration improved nonalcoholic steatohepatitis score, attributed to decreased microvesicular steatosis. In conclusion, endogenous FGF-21 confers some protection against obesity-induced inflammation, and low-dose FGF-21 administration decreases hepatic steatosis independent of changes in body weight.

Supported By: Georgia State University

TLR4-Induced Local Adipose Inflammation Critically Regulates Glucose Homeostasis

SHANGANG ZHAO, PHILIPP E. SCHERER, Dallas, TX

Acute adipose inflammation is beneficial for adipose tissue remodeling, while chronic uncontrolled inflammation may lead to systemic insulin resistance. Toll-like receptor 4 (TLR4) may be an important mediator for obesity-associated chronic low grade inflammation and insulin resistance. However, up to date, we do not have a model available that allows us to study systemic consequences of adipose tissue inflammation originating selectively at the level of the adipocyte. Here, using cre-lox and dioxycycline-inducible system, we generated a new mouse model, which exclusively expresses physiological levels of TLR4 in adipocytes of adult mice in the background of an otherwise global TLR4 null mouse (“ATLR4 mice”). Upon LPS injection, ATLR4 mice show moderate acute inflammation in local adipose tissue, but no inflammatory response at the systemic level. However, when exposed long-term to a HFD diet, ATLR4 mice show reduced body weight gain as well as improved glucose and insulin tolerance. This beneficial effect may - at least in part - be due to increased browning of subcutaneous white adipocytes. Under thermoneutral conditions (when we minimize the contributions of the browning effects), the ATLR4 mice show a slightly higher body weight gain, but still preserve better glucose tolerance. RNAseq data indicates the beneficial effect of ATLR4 mice may be associated with enhancing acetyl-CoA synthesis pathway to promote PPARgamma acetylation and adipogenesis. Based on these results, we conclude that adipose tissue inflammation originating in the adipocyte contributes only minimal, if any, effects on systemic inflammation. In contrast, TLR4-induced local inflammation signaling results in improvements in glucose homeostasis.

Supported By: National Institutes of Health (P01DK089788), Fonds de recherche du Québec

Insulin Action on Endothelial Cells Limits Leukocyte-Endothelial Interaction through CXCR4 and Counteracts Intestinal Tumor Formation in Obesity

THOMAS RATHJEN, QIAN LI, KYOUNGMIN PARK, GRO POVLSEN, GRIFF SKYTTÉ, OLSEN, GEORGE L. KING, CHRISTIAN RASK-MADSSEN, Berlin, Germany; Boston, MA; Måln, Denmark

An activated, pro-inflammatory endothelium is a key feature of obesity and type 2 diabetes but little is known about its contribution to the increased cancer risk in these conditions. We recently published that insulin resistance in endothelial cells increases VCAM-1 expression, increases recruitment of tumor-associated neutrophils and promotes intestinal tumor formation. Here, we report that tumor-prone Apo<sup>r</sup>M1/+ mice have 2.1-fold more intestinal tumors during high-fat feeding. However, gain of insulin signaling specifically in endothelial cells by overexpression of IRS1 prevented 44% of tumors in diet-induced obesity. RNA sequencing in primary human endothelial cells identified 17 genes changed by insulin treatment with a log 2 change of at least ±0.5, among them C-X-C motif chemokine receptor 4 (CXCR4), which was downregulated by 94%. Downregulation of CXCR4 after insulin treatment was completely prevented by pretreatment with wortmannin but not by U0126, an inhibitor of MAPK signaling. Using FACS of enzymatically dissociated tissue, CXCR4 mRNA in CD31+ cells was 77% higher in mice with diet-induced obesity compared to lean controls and 37% higher in db/db mice compared to db/+ controls, consistent with upregulation of CXCR4 in endothelial cell insulin resistance. CXCL12, the ligand for CXCR4, increased leukocyte adhesion to cultured endothelial cells and this was completely prevented by plerixafor, a clinically approved CXCR4 antagonist. In vivo microscopy of mesenteric venules showed an increase in leukocyte rolling and adhesion after intravenous injection of CXCL12 and this change was abrogated in transgenic mice with endothelial overexpression of IRS1. We conclude that endothelial cell insulin signaling limit leukocyte-endothelial cell interaction through downregulation of CXCR4 and that improving insulin signaling in endothelial cells may protect against tumor development in obesity.

Supported By: ADA-Supported Research

Adipocyte-Selective Deletion of β-Arrestin-1 in Mice Causes Adiposity, Impaired Glucose Tolerance, and Reduced Insulin Sensitivity

SAI PRASAD PYDI, JÜRGEN WESS, Bethesda, MD

In obese individuals, excess fat accumulates in adipose tissue (AT), leading to altered AT metabolism and increased insulin resistance, a key feature of type 2 diabetes (T2D). Therefore, it is of great importance to understand the signaling pathways that regulate AT function. Activation of certain G protein-coupled receptors (GPCRs) in AT has been reported to have beneficial effects on whole body glucose homeostasis. GPCR signaling is modulated by β-arrestin-1 and -2 (bar1 and bar2, respectively), two intracellular proteins which can terminate GPCR signaling and/or mediate G protein-independent signaling. The two β-arrestins are known to regulate many important physiological functions, primarily based on work with whole body knockout (KO) mice. The potential roles of bar1 and bar2 in regulating adipocyte function in vivo remain unexplored. To address this issue, we used Cre-lox technology to generate mutant mice that lacked bar1 selectively in adipocytes (adipo-bar1<sup>−/−</sup>) and bar2 selectively in adipocytes (adipo-bar2<sup>−/−</sup>). Interestingly, adipo-bar1<sup>−/−</sup> mice maintained on a high-fat diet showed significantly increased body weight and adiposity, impaired glucose tolerance, and reduced insulin sensitivity. Moreover, blood glucose and plasma insulin levels were elevated in adipo-bar1<sup>−/−</sup> KO mice, but not by U0126, an inhibitor of MAPK signaling. Using FACS of enzymatically dissociated tissue, CXCR4 mRNA in CD31+ cells was 77% higher but not by U0126, an inhibitor of MAPK signaling. Using FACS of enzymatically dissociated tissue, CXCR4 mRNA in CD31+ cells was 77% higher in mice with diet-induced obesity compared to lean controls and 37% higher in db/db mice compared to db/+ controls, consistent with upregulation of CXCR4 in endothelial cell insulin resistance. CXCL12, the ligand for CXCR4, increased leukocyte adhesion to cultured endothelial cells and this was completely prevented by plerixafor, a clinically approved CXCR4 antagonist. In vivo microscopy of mesenteric venules showed an increase in leukocyte rolling and adhesion after intravenous injection of CXCL12 and this change was abrogated in transgenic mice with endothelial overexpression of IRS1. We conclude that endothelial cell insulin signaling limit leukocyte-endothelial cell interaction through downregulation of CXCR4 and that improving insulin signaling in endothelial cells may protect against tumor development in obesity.

Supported By: ADA-Supported Research

The Metabolic Effect of Chronic Elevated Erythropoietin in Tg6 Mice

HEATHER ROGERS, OKSANA GAVRILOVA, CONSTANCE T. NOGUCHI, SAI PRASAD PYDI, JÜRGEN WESS, Bethesda, MD

Erythropoietin (EPO) is the cytokine required for erythroid production. However, EPO receptor (EpoR) expression is not restricted to erythroid tissue and non-erythropoietic EPO action has been associated with the regulation of glucose homeostasis and fat mass accumulation in animal models. The hemizygous transgenic tg<sub>6</sub> mouse (PODGFR-promoter/human EPO cDNA) overexpresses EPO, allowing for the study of chronic elevated levels of EPO. Tg6 mice exhibit a hematocrit of 80-90%, almost twice that of their wild type
Insulin Resistance

The “westernized” diet reduces brain dopamine synthesis and low brain striatal dopamine function has been associated with and implicated in potentiation of metabolic syndrome in animals and humans. However, hypothalamic dopamine function may be a more dominant regulator of peripheral fuel metabolism. The hypothalamic SuMN dopaminergic neurons project to the lateral septum, medial preoptic area, and suprachiasmatic nucleus, areas that prominently regulate both peripheral metabolism and striatal dopamine function. However, a causal role for such hypothalamic dopaminergic circuitry in modulating peripheral metabolism under normal feeding conditions has never been explored. This study therefore tested the impact of SuMN-selective knock-down of tyrosine hydroxylase (TH, the rate-limiting enzyme for dopamine synthesis) gene expression using SuMN-mediated shRNA targeting TH (AAV-TH shRNA) on peripheral fuel metabolism in 14 weeks old rats fed standard low fat rodent chow (RC). Rats were micro-infused at the SuMN with either AAV-TH shRNA (N=12) or AAV-scrambled shRNA (control) (N=10) and maintained on RC ad lib for 77 days to assess changes in body weight (BW), glucose tolerance and fat metabolism. SuMN-selective TH knock down increased BW gain (54%, p=0.0005), total white adipose tissue mass (43%, p=0.012), feed efficiency (BW gain /g food) (25%, p=0.048) and cumulative food consumption (15%, p= 0.0001) vs. control. Such knock down also reduced adipose tissue mitochondrial fatty acid oxidation (FAO) rate (basal oxygen consumption rate 51%, p=0.99) vs. control. Such knock down also reduced adipose tissue mitochondrial fatty acid oxidation (FAO) rate (basal oxygen consumption rate 51%, p=0.99) vs. control. Such knock down also reduced adipose tissue mitochondrial fatty acid oxidation (FAO) rate (basal oxygen consumption rate 51%, p=0.99) vs. control. These findings indicate that reduced SuMN dopaminergic neuronal activity facilitates dysglycemia and obesity while reducing fat energy expenditure and increasing food consumption.

Results: Perigonadal white AT (PWAT) and body weight were not significantly different between KO and control groups but liver weight and liver-to-body weight ratio were significantly reduced in obese K0 mice (p<0.05). STAT1 KO mice on HFD exhibited improved insulin sensitivity examined by insulin tolerance test (p<0.05) and reduced expression of inflammatory markers TNFα, IFNγ, IL-12 and MCP1 in PWAT and subcutaneous AT (SAT) compared to littermate controls (p<0.05). AT immune cell analysis revealed that STAT1 ablation caused a decrease in M1-like proinflammatory polarization and increase in M2-like polarization of F4/80+ macrophages, reduced number of total CD3+ T cells and CD8+ T cells in PWAT. In addition, brown/beige adipogenesis markers UCPI, CIDEA and Prdm16 were also upregulated (p<0.05) in SAT of obese K0 mice.

Conclusion: Our results show the critical role of macrophage/dendritic cell STAT1 in obesity-induced AT inflammation and insulin resistance.

Supported By: American Diabetes Association (17-1BS-082 to H.W.) National Institutes of Health American Heart Association

2037-P

Silencing of Supramamillary Nucleus (SuMN) Dopaminergic Neuronal Activity Induces the Obese Glucose Intolerant State

YAHONG ZHANG, TSUNG-HUANG TSAI, MICHAEL EZROKHI, CARL STOEZEL, ANTHONY DICHOTA, TX

Background: Obesity is a global epidemic and major risk factor for insulin resistance and type 2 diabetes. Obesity is associated with low grade chronic inflammation of adipose tissue (AT). F4/80+CD11c+ macrophages/dendritic cells are increased and polarized into M1-like phenotypes in AT and may contribute to insulin resistance in mouse models of obesity. STAT1 is a transcription factor that play key roles in macrophage polarization into M1-like phenotypes. Hence, we investigated the role of CD11c+ macrophage/dendritic cell STAT1 in obesity-induced AT inflammation and insulin resistance.

Methods: Mice with specific knockout of STAT1 in CD11c+ cells were generated by crossbreeding STAT1 fl/fl and CD11c-Cre mice. CD11c/LSTAT1 KO and littermate controls were fed either high fat or normal diet (ND) to lean controls. We evaluated body composition, insulin sensitivity, gene expression of inflammatory markers, various immune cells and brown/beige adipogenesis markers in AT.

2038-P

SRC-2 in POMC Neurons Mediates Energy Reserving Effects of FoxO1

YOUNG JAE YANG, YONG XIU, Houston, TX

The nuclear receptor coactivator, steroid receptor coactivator-2 (SRC-2) is an essential for body weight control. However, the molecular mechanisms by which SRC-2 regulates energy homeostasis are not fully understood. Here we showed that SRC-2 is highly expressed by hypothalamic pro-opiomelanocortin (POMC) neurons. We then generated mice lacking SRC-2 selectively in POMC neurons. These mutant mice were more resistance to high fat-diet-induced obesity compared to wild type littermates. In addition, we observed that the mutant mice failed to properly suppress energy expenditure during food deprivation, refedding response after fasting was impaired in these mutant mice, which was accompanied with increased POMC gene expression in the hypothalamus, increased firing rate, and decreased mPSE amplitude of POMC neurons. Further anxiety-like behavior tests showed the mutant mice exhibited decreased motivational state and incentive salience of the food reward, and enhanced Dopamine signaling to POMC neurons. Interestingly, SRC-2 interacts with FoxO1 in mouse hypothalamus, and this interaction was enhanced by fasting. Finally, using luciferase assay, we showed that over-expression of SRC-2 significantly suppressed POMC expression. Collectively, our results indicate that SRC-2 in POMC neurons, as a nuclear receptor coactivator, interacts with FoxO1 to amplify its transcription suppressing effects on the POMC gene, and therefore mediates the energy reserving effects of FoxO1 during food deprivation.

2039-P

Challenging the Adipocyte Color Barrier—TR Activation Elicits White to Beige Transdifferentiation Independent of Beta-Adrenergic Signaling

YAN XIA, XIANGFEI LUANG, MARK E. LEE, KEVIN PHILLIPS, Houston, TX

Induction of beige adipocytes, or brown-like adipocytes, in white adipose tissues (WAT) has become an alluring possibility to combat diabetes and metabolic diseases. Beige adipocytes express abundant UCP1 protein, exert energy dissipating and thermogenic functions similar to brown adipocytes. In this study, we compared the beiging effects of a synthetic thyroid hormone receptor (TR) agonist, GC1, with the beta-adrenergic receptor (β-AR) agonist CL316243, which is generally accepted as the most efficacious beiging agent, and explored mechanistic similarities and distinctions between the two compounds in a variety of in vitro cell models.

Here we show that GC1 induces beiging, in cultured adipocytes derived from inguinal WAT, to a much greater extent than CL316243; in addition, TR activation by GC1 is sufficient to induce beiging in a variety of vescively derived white adipocytes, as well as 3T3-L1 cells, actions which CL316243 is incapable of. Both GC1 and CL316243 increased expression of ATGL and p-HSL, two key lipases known to be necessary for the activation of UCP1-meditated uncoupling and thermogenesis, although GC1 increased these proteins to a higher extent. Enzymes involved in lipid beta-oxidation, such as ACC/p-ACC and LCAD, are also much more markedly enhanced in GC1-treated cells than those treated with CL316243. Interestingly, the loss of all β-ARs, does not affect the ability of TR activation to elicit beiging, demonstrating that TR agonism induces beiging by novel mechanisms that are independent of beta-adrenergic signaling. Thus, select TR agonists appear to be sufficient to elicit beiging in a fashion that appears to be mechanistically distinct from perhaps all other known beiging agents (nearly all of which require β-AR signaling), making them important tools in assessing the therapeutic potential of beige fat activation to treat diabetes and metabolic disease.
Nr4a1 and Nr4a3 Knock Out Mice Have Impaired Glucose Clearance and Beta-Cell Function under High-Fat Feeding

COURTNEY J. SMITH, KYLE B. KENER, JEFFERY S. TESSEM, Provo, UT

We have shown that the orphan nuclear receptors Nr4a1 and Nr4a3 are critical for beta cell mitochondrial respiration and fuel utilization, and that loss of either factor impedes fuel utilization and insulin secretion. We have also demonstrated that prolonged culture of INS-1 832/13 beta cells with progressively increasing concentrations of palmitic acid results in decreased Nr4a1 and Nr4a3 expression, impaired mitochondrial respiration, and reduced insulin secretion. Here we explore the effect of 20-week high fat diet on wild type mice and mice deficient for either Nr4a1 or Nr4a3. Nr4a1 and Nr4a3 knock out mice have greater body weight than wild type animals when on a high fat diet. Mice deficient for Nr4a1 or Nr4a3 have no significant change in non-fasting blood glucose measurements as compared to wild type under normal chow conditions. Non-fasting blood glucose was elevated in both Nr4a1 and Nr4a3 knock out mice under high fat feeding conditions. Fasting glucose tolerance tests also demonstrate that Nr4a1 and Nr4a3 knock out mice have impaired glucose tolerance as compared to wild type animals under high fat feeding. Mitochondrial respiration of muscle, liver, adipose and islets are impaired as compared to wild type controls under high fat feeding. Glucose stimulated insulin secretion is impaired in islets from Nr4a1 or Nr4a3 knock out mice fed a high fat diet. These data demonstrate changes in various metabolic tissues as a result of high fat feeding and deletion of the Nr4a orphan nuclear receptors, demonstrating that they play a critical role in systemic fuel utilization.

Supported By: American Diabetes Association (1-17-IBS-101 to J.S.T.)

Resistin Is Associated with Blood-Brain Barrier Disruption in Mice Resistant to Diet-Induced Obesity and Treated with Topiramate

THERESE S. SALAMEH, WILLIAM MORTELL, WILLIAM A. BANKS, Seattle, WA

Resistin has been linked to diabetes, obesity, insulin resistance, atherosclerosis, and the development of cardiovascular disease. However, the effects and the molecular mechanisms of resistin on endothelial permeability, a key event in the development of atherosclerosis, inflammation, and vascular disease, have not been fully elucidated. Diabetes is associated with changes in the brain microvasculature leading to dysfunction and disruption of the blood-brain barrier (BBB), a specialized system of microvascular endothelial cells protecting the brain from toxic substances in circulation, while permitting CNS entry of nutrients and endocrine signals using active transport mechanisms and passive diffusion. As diabetes is associated with cognitive impairment, understanding the molecular mechanisms of endothelial permeability in the brain is important in developing appropriate therapeutic agents. Topiramate (TPM), a mitochondrial carbonic anhydrase inhibitor, prevents BBB disruption in mouse models of type 1 and 2 diabetes. Mice resistant to the development of diet-induced obesity, when treated with TPM, had increased serum levels of resistin and increased BBB permeability to all brain regions except the hippocampus and hypothalamus, brain regions paradoxically disrupted in models of type 2 diabetes. In vitro treatment of brain endothelial cells with resistin demonstrated a decrease in endothelial nitric oxide synthase (eNOS) along with increased permeability and decreased TEER, a measure of electrical resistance across a cell monolayer. This increase in permeability occurs because diet-resistant mice treated with TPM are unable to attenuate the effects of hyperglycemia-induced oxidative stress and inflammation. Topiramate, which is protective of the BBB in types I and II diabetes, seems paradoxically toxic to the BBB in mice resistant to diet-induced obesity and this toxicity is associated with increases in serum resistin.

Supported By: National Institutes of Health
Preoperative Hemoglobin A1c Predicts Postoperative Weight Loss Following Bariatric Surgery in Patients with Diabetes

CARRILA B. ORTEGA, HUI-JIE LEE, DANA PORTENIER, ALFREDO D. GUERRON, JENNY TONG, Durham, NC

Consensus on whether preoperative (pre-op) hyperglycemia predicts adverse surgical outcomes is lacking. The objective of the study was to evaluate the relationship between pre-op HbA1c and postoperative (post-op) surgical outcomes in patients with diabetes mellitus (DM). Patients who underwent bariatric surgery between January 2000 and April 2017 and met the diagnostic criteria of DM and had pre-op HbA1c measures were studied. Logistic and GEE linear regression were used to examine the association between pre-op HbA1c and post-op morbidity and mortality and percentage weight loss (%WL) at 30 days and 1 year. A total of 2173 patients (mean age 48.6 ± 10.6, pre-op weight: 297.5 ± 60.3 lb, 75% females) were evaluated. Among them, 49.6% had HbA1c of <7%, 26.4% had HbA1c 7-8%, and 23.9% had HbA1c >8%. The incidence of 30-day complications (readmission, reoperation, bleeding, pulmonary embolism, leak) was 6.1% and 30-day mortality was 0.1%. These rates did not differ between HbA1c groups or between Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG), gastric band, and duodenal switch (DS) procedures. There was no significant association between pre-op HbA1c and complication rates or %WL at 30 days post-op. However, we detected an association between HbA1c and 1-year %WL (p = 0.014) in that 1% increase in pre-op HbA1c was associated with 0.74% less WL at 1 year after adjusting for confounders (95% CI: -1.08% to -0.41%, p < 0.0001). Females lost less weight than males (p = 0.0009) and patients with ≥ 1 anti-hypertensive medications pre-op lost less weight than those without (p < 0.0001) at 1 year. Furthermore, patients operated with DS lost more while those with SG and banding lost less weight than with RYGB.

In conclusion, pre-op HbA1c was not associated with post-op morbidity or mortality but it is a significant predictor for post-op WL at 1 year. Our data suggest that tighter glycemic control pre-op may lead to better weight loss outcomes after bariatric surgery in patients with DM.

Acarbose and Pasireotide Reduce Hypoglycemia in Roux-en-Y Gas- troscopic Bypass Operated Subjects

CAROLINE B. ORTEGA, URR KIELGAST, SR., JENS J. HOLST, DORTE WORM, JENNY TONG, Durham, NC

Introduction: Hypoglycemia is a severe complication after Roux-en-Y gastric bypass (RYGB), with no effective treatment options. We investigated the glucose stabilizing effects of five therapeutic agents in RYGB operated tric bypass (RYGB), with no effective treatment options. We investigated

CAROLINE ØHRSTRÔM, URD KIELGAST, SR., JENS J. HOLST, DORTE WORM, JENNY TONG, Durham, NC

Acarbose and Pasireotide Reduce Hypoglycemia in Roux ‑en‑Y Gas‑ troscopic Bypass Operated Subjects

CAROLINE B. ORTEGA, URR KIELGAST, SR., JENS J. HOLST, DORTE WORM, JENNY TONG, Durham, NC

Introduction: Hypoglycemia is a severe complication after Roux-en-Y gastric bypass (RYGB), with no effective treatment options. We investigated the glucose stabilizing effects of five therapeutic agents in RYGB operated tric bypass (RYGB), with no effective treatment options. We investigated

baseline mean age 43±12 years, T1 duration 22±11 years, Hba1c 8.4±0.1%, BMI 43.9±6.3 kg/m², weight 116.1±19.3 kg, systolic BP 123±17 mmHg, dia- stolic BP 71±8 mmHg, LDL-C 81±22 mg/dL, HDL-C 57±20 mg/dL, triglycerides 103±62 mg/dL. T1 was confirmed based on the presence of antibodies, his- tory of DKA and clinical criteria. There were no differences between cohorts at baseline, except that more patients used insulin pump therapy in the BS cohort (65% vs. 35%, p=0.05).

At 3 years, body weight changed by -33.5±2.6 kg (-28.1±2.2%) in the BS cohort and by +2.6±2.8 kg (+2.2±2.4%) in the matched cohort (p=0.0001). However, Hba1c, BP and LDL-C did not change from baseline in both cohorts. HDL-C increased and triglycerides decreased in the BS cohort in comparison to the matched cohort (p=0.05 for both).

These results show that despite significant reduction in body weight and improvements in HDL-C and triglyceride levels, bariatric surgery has no long‑term impact on glycemic control, BP and LDL-C in patients with T1 and obesity.

Results: BMD was correlated with 25OHD (r=0.3, p=0.02), phosphate (r=0.3, p=0.04), M (n=0, p=0.008), dietary calcium (n=3, p=0.3) and dietary phosphate (n=3, p=0.04) after adjustments for age, sex and BMI. There were no differences in BMD, 25OHD, calcium, phosphate, PTH, FGF-23, alkaline phosphatase (ALP), high‑sensitivity C‑reactive protein (hs‑CRP), lipid profile were measured and physical activity and dietary calcium and phosphate intake were calculated based on self-report and validated ques- tionnaires.

Results: BMD was correlated with 25OHD (r=0.3, p=0.02), phosphate (r=0.3, p=0.04), M (n=0, p=0.008), dietary calcium (n=3, p=0.3) and dietary phosphate (n=3, p=0.04) after adjustments for age, sex and BMI. There were no differences in BMD, 25OHD, calcium, phosphate, PTH and FGF-23 levels between insulin-sensitive and insulin-resistant groups (insulin sensi- tivity (M) cut-off of 4.7 mg/kg/min, all p>0.5). However, ALP was signifi- cantly higher in the insulin-resistant group (86.28 vs. 72.92 IU/L, p=0.04). In regression analyses, 25OHD (p=0.02), phosphate (p=0.01), BM (p=0.02) and M (p=0.02) remained independently related to BMD.

Conclusion: Insulin sensitivity and phosphate levels in addition to BMI and 25OHD were related to BMI in this overweight/obese and vitamin D-deficient population. These findings provide further evidence supporting an independent role for insulin sensitivity in bone health.

Supported By: National Health and Medical Research Council of Australia (1047897 to B.D.C.)

Insulin Sensitivity Is an Independent Determinant of Bone Mineral Density in Overweight and Obese Individuals

NEDAR NAGERSPOOR, AYA MOLSA, BARBARA DE COURTEN, Melbourne, Australia

Background: Higher BMI and 25-hydroxyvitamin D (25OHD) levels are associated with higher bone mineral density (BMD). However, obese indi- viduals are more likely to be vitamin D-deficient. This is limited data on other factors influencing BMD in the obese population.

Methods: We examined the cross-sectional relationship between BMD and anthropometric, biochemical, markers, in addition to dietary calcium and phosphate intake and physical activity in 54 overweight or obese but otherwise healthy adults (35 males, 19 females) with 25(OH)D<50 nmol/L, BMD, body mass index (BMI), percent body fat (PFT), fat mass and lean mass (dual energy x-ray absorptimetry), insulin sensitivity (euglyce‐ mia-hyperinsulinemic clamp, M), 25OHD, calcium and phosphate, PTH, FGF-23, alkaline phosphatase (ALP), high-sensitivity C-reactive protein (hs-CRP), lipid profile were measured and physical activity and dietary calcium and phosphate intake were calculated based on self-report and validated ques- tionnaires.

Results: BMD was correlated with 25OHD (r=0.3, p=0.02), phosphate (r=0.3, p=0.04), M (n=0, p=0.008), dietary calcium (n=3, p=0.3) and dietary phosphate (n=3, p=0.04) after adjustments for age, sex and BMI. There were no differences in BMD, 25OHD, calcium, phosphate, PTH and FGF-23 levels between insulin-sensitive and insulin-resistant groups (insulin sensi- tivity (M) cut-off of 4.7 mg/kg/min, all p>0.5). However, ALP was signifi- cantly higher in the insulin-resistant group (86.28 vs. 72.92 IU/L, p=0.04). In regression analyses, 25OHD (p=0.02), phosphate (p=0.01), BM (p=0.02) and M (p=0.02) remained independently related to BMD.

Conclusion: Insulin sensitivity and phosphate levels in addition to BMI and 25OHD were related to BMI in this overweight/obese and vitamin D-deficient population. These findings provide further evidence supporting an independent role for insulin sensitivity in bone health.

Supported By: National Health and Medical Research Council of Australia (1047897 to B.D.C.)

Insulin Resistance and In Vivo Lipolytic Rate Are Positively Associ- ated with Body Iron Stores in Obese Women

BENJAMIN J. RYAN, DOUGLAS W. VAN PELT, LISA M. GUTH, ALISON LUDZKI, RACHEL A. GIUSCIA-RYAN, CHIWOON AHN, JEFFREY F. HOROWITZ, Ann Arbor, MI

High body iron stores are positively related to insulin resistance in humans, but the underlying mechanisms remain unresolved. Iron stimu- lates lipolysis in murine adipocytes in vitro, but the influence of iron stores on lipolytic rate in vivo is unknown. Our aim was to determine if body iron stores are associated with lipolytic rate and whole-body insulin sensitivity in obese, pre-menopausal women. We studied 20 subjects with clinically- normal (20-200 ng/mL) plasma [ferritin], an index of body iron stores. Fatty acid rate of appearance into systemic circulation (FA Ra) was assessed by 13C-palmitate isotope dilution, insulin resistance was assessed by hyperin- sulinemic-euglycemic clamp, and abdominal subcutaneous adipose tissue protein expression was assessed via immunoblot. [Ferritin] was significantly (p < 0.01), positively correlated with FA Ra (r = 0.42), adipose hormone sensi- tive lipase(ADHSL) phosphorylation (p-HSLser660), a marker of lipolytic activation in adipose tissue; r² = 0.41), and whole-body insulin resistance (r² = 0.33). Importantly, [Ferritin] remained a significant, independent predictor for these parameters in multiple regression models including body mass index, plasma [adiponectin], and plasma [CRP] as covariates. We stratified subjects into tertiles based on [Ferritin] to compare high-normal and low-normal [Ferritin] groups (138 ± 30 vs. 40 ± 15 mg/mL). Compared with the low-normal [Ferritin]...
Stimulation of the β3-Adrenergic Receptor via Mirabegron Induces Lipolysis and Thermogenesis in Human Adipocytes

CHERYL CERO, ALANA O'MARA, JAMES W. JOHNSON, ALISON S. BASKIN, JOYCE D. LINDERMAN, AARON CYPESS, Bethesda, MD

In rodent models, the β3-adrenergic receptor (AR) is responsible for thermogenesis in brown adipose tissue (BAT) and lipolysis in white adipose tissue (WAT). In contrast, the contribution of β3-AR in human adipocytes is controversial due to the low expression of the β3-AR in WAT and access only to partial β3-AR agonists. Mirabegron, an FDA-approved drug for overactive bladder, is a selective human β3-AR agonist. In a recent clinical trial, mirabegron activated human BAT thermogenesis and WAT lipolysis. Therefore, we investigated the distribution and relative contribution of β3-AR (i) in white (hWAT) and brown (hBAT) adipose tissue from human autopsies and (ii) immortalized human white (hWA) and brown (hBA) adipocytes. Among the three β-ARs, β3-AR and β2-AR are similarly expressed in brown and white adipose tissue, whereas β3-AR is the highest expression in hBAT. In immortalized differentiated cells, hBA have a significantly higher expression of β3-AR compared to hWA. To assess the functionality of these receptors in adipocytes, dose-response curves of agonist-stimulated lipolysis were investigated in differentiated human and mouse adipocytes. We observed that stimulation of any one of the three β-ARs in human adipocytes induces a significant increase in glycerol release, a lipolytic byproduct. However, the effective dose of mirabegron to activate β3-AR-mediated lipolysis in white and brown adipocytes via mirabegron was significantly lower (hWA: EC50 2.55E-09; hBA: EC50 6.31E-09) compared to specific activators of β1-AR or β2-AR.

In summary, we identify a major role played by the β3-AR in the regulation of human BAT thermogenesis and WAT lipolysis, both in vivo and in vitro. Due to the comparatively minimal effects of mirabegron treatment on the cardiovascular system, selective β3-AR agonists may be the optimal choice for targeted stimulation of human WAT and BAT.

Supported By: National Institutes of Health

Effects of Different Types of Oral Glucose-Lowering Drugs on Hepatic Fat Accumulation and Liver Function in Japanese Subjects with Type 2 Diabetes Mellitus and Nonalcoholic Fatty Liver Disease—A Randomized, Open-Label, 3-Arm Active-Control Study

TOMOYUKI KINOSHITA, MASSASHI SHIMODA, SHOHEI NAKANISHI, TOMIYASU MUNE, KOHEI KAKU, HIDEAKI KANETO, Kurashiki, Japan

Objective: In this study, we compared the effects of different types of oral hypoglycemic agents on NAFLD in subjects with T2DM.

Methods: We conducted a randomized, open-label, 3-arm active-control trial in subjects with T2DM and NAFLD. A total of 98 subjects were randomly allocated either to dapagliflozin (SG, n=32), pioglitazone (TZ, n=33) or glimepiride (SU, n=33) group, and the subjects took these drugs for 28 weeks. The primary endpoint was a change of liver-to-spleen (L/S) ratio on CT.

Results: Baseline characteristics in the three groups were similar in various clinical parameters. SG, TZ and SU ameliorated glycemic control similarly. Body weight and visceral fat area (VFA) were significantly decreased only in SG group. Serum adiponectin level was increased in TZ group compared to control but not SU, significantly increased L/S ratio and decreased ALT level, and the effects of SG and TZ on those parameters were comparable. In simple correlation analysis with all subjects, change of L/S ratio was negatively correlated with alteration of BMI, VFA, HbA1c and serum insulin, and positively associated with change of adiponectin level. Multiple linear regression analysis revealed that the decrease in VFA and the increase in adiponectin level contributed to improvement of NAFLD in subjects with T2DM. In addition, the common factor which improved NAFLD in all groups was reduced VFA. On the other hand, there were also some differences among three groups about which factors were correlated with the change of L/S ratio.

Conclusions: The present study showed the decreased VFA and increased adiponectin independently contributed to improve NAFLD in patients with T2DM. Furthermore, dapagliflozin and pioglitazone, exerted equivalent beneficial effects on NAFLD in subjects with T2DM, although the two drugs have different mechanism of action.

Supported By: American Diabetes Association (16-1CTS-048) to J.F.H. National Institutes of Health (R01DK07996, T32DK007245, P30DK089503, UL1TR000433)

Obesity—Human

β3-adrenergic receptor (AR) is responsible for thermogenesis in brown adipose tissue (BAT) and lipolysis in white adipose tissue (WAT). In contrast, the contribution of β3-AR in human adipocytes is controversial due to the low expression of the β3-AR in WAT and access only to partial β3-AR agonists. Mirabegron, an FDA-approved drug for overactive bladder, is a selective human β3-AR agonist. In a recent clinical trial, mirabegron activated human BAT thermogenesis and WAT lipolysis. Therefore, we investigated the distribution and relative contribution of β3-AR (i) in white (hWAT) and brown (hBAT) adipose tissue from human autopsies and (ii) immortalized human white (hWA) and brown (hBA) adipocytes. Among the three β-ARs, β3-AR and β2-AR are similarly expressed in brown and white adipose tissue, whereas β3-AR is the highest expression in hBAT. In immortalized differentiated cells, hBA have a significantly higher expression of β3-AR compared to hWA. To assess the functionality of these receptors in adipocytes, dose-response curves of agonist-stimulated lipolysis were investigated in differentiated human and mouse adipocytes. We observed that stimulation of any one of the three β-ARs in human adipocytes induces a significant increase in glycerol release, a lipolytic byproduct. However, the effective dose of mirabegron to activate β3-AR-mediated lipolysis in white and brown adipocytes via mirabegron was significantly lower (hWA: EC50 2.55E-09; hBA: EC50 6.31E-09) compared to specific activators of β1-AR or β2-AR.

In summary, we identify a major role played by the β3-AR in the regulation of human BAT thermogenesis and WAT lipolysis, both in vivo and in vitro. Due to the comparatively minimal effects of mirabegron treatment on the cardiovascular system, selective β3-AR agonists may be the optimal choice for targeted stimulation of human WAT and BAT.

Supported By: National Institutes of Health

The Existence of Superficial Dorsocervical Brown Adipose Tissue in Women

LAURA FLETCHER, BROOKS LEITNER, KATHERINE J. KIM, SUZANNE MCGEEHER, ROBERT BRYCHTA, AARON CYPESS, KIYI Y. CHEN, Bethesda, MD

Background: Cold stimulation of human brown adipose tissue (BAT) can increase its glucose uptake and energy expenditure, making it a potential target for treating obesity and metabolic disease. BAT is commonly found in deeper fascial layers of specific depots. We observed a distinct sexual dimorphism in the dorsal side of the cervical BAT depot.

Methods: Twenty-one healthy, lean, young subjects (12 men, mean BMI 23 ± 2.1 kg/m2), were exposed to five hours of tolerable cold exposure. BAT was measured by 18F-FDG PET/CT.

Results: Men and women had similar total BAT metabolic activity. We classified the cervical BAT depot into two distinct anatomically continuous areas: a deeper, intermuscular region, and a superficial, dorsocervical region (sdBAT). sdBAT was present in 6 women, but only in one man (Figure C). Women had less lean mass than men (p<0.001). In women, individual sdBAT metabolic activity was negatively correlated with lean body mass (r=-0.59) and positively correlated with total and cervical BAT (pcor=0.04).

Conclusions: We believe that sdBAT in women is likely part of the same fascial layer as the classical cervical depot. But based on its location, the sdBAT depot could be a remnant of interscapular BAT seen in rodents and human newborns. These findings are consistent with a model in which the dominant source of thermogenesis is lean tissue, which is lower in women, and when insufficient leads to BAT activation.

Supported By: National Institutes of Health (R01DK077966, T32DK007245, P30DK089503, UL1TR000433)
In conclusion, the levels of circulating adipokines in patients with type 2 diabetes are related in varying degrees with body fat distribution and AT microvasculature. The relationships between serum levels of adipokines, body fat distribution, and subcutaneous microvasculature in type 2 diabetic subjects. The aim of the study: to determine the relationships between serum levels of adipokines, body fat distribution, density and ultrastructure of blood and lymphatic microvessels in subcutaneous adipose tissue (AT) in type 2 diabetic subjects. We observed 125 patients with type 2 diabetes, including 82 subjects with obesity, and 30 lean nondiabetic individuals matched by sex and age. The concentrates of leptin, resistin, visfatin, adipin, and adiponectin in the fasting serum were determined by Multiplex analysis. The fat mass and AT distribution was assessed by DXA. The samples of subcutaneous abdominal AT were obtained with the knife biopsy in 25 patients and in 15 healthy subjects. Immunohistochemistry for biomarkers CD-34, podoplanin (D2-40) and LYVE-1 was applied to identify the blood and lymphatic microvessels. The volume density, numeral density and ultrastructure of blood and lymphatic microvessels were assessed. Patients with diabetes, as compared to control, had significantly higher levels of leptin (p=0.004), resistin (p<0.0001), adipin (p<0.0001) and visfatin (p=0.0003). The concentrations of leptin and adipin were associated with total, truncal, android and gynoid fat mass. The levels of resistin and adiponectin demonstrated relationships with gynoid fat mass only. In obese diabetic subjects an increase in the volume and numeral density of podoplanin-expressing lymphatic vessels was observed. The swelling of cytoplasm, mitochondria, rough endoplasmic reticulum and reduced content of microprotoplasmic vesicles was revealed in lymphatic capillaries. The levels of leptin and adipin, but not resistin and visfatin levels, correlated negatively with the numeral density of microvessels in subcutaneous AT (r=0.53 and r=0.32 respectively).

In conclusion, the levels of circulating adipokines in patients with type 2 diabetes are related in varying degrees with body fat distribution and AT microvesSEL density.
Five-Year Glycemic and Metabolic Outcomes after Bariatric Surgery in an Asian Population with Type 2 Diabetes

ZHONG HONG LIU, AYE CHAN MAUN, SONALI GANGULY, PHONG CHING LEE, KWANG-WEE THAM, Singapore, Singapore

Background: Metabolic-bariatric surgery (MBS) leads to durable weight loss and significant metabolic improvement in type 2 diabetes mellitus (T2DM) patients with obesity. However, data on durability of control is often lacking in Asia.

Aim: We report 5-year glycemic and metabolic outcomes in a T2DM cohort who had MBS from 2008-2012 at a tertiary center in Singapore.

Methodology: Patient demographics and biochemical parameters were retrieved from a web-based data repository. DM remission was defined as HbA1c ≤ 6% without DM medications.

Results: There were 59 patients with a mean age of 43.0±9.5 years and 37.3% were males (Table 1). Most (76.3%) had gastric bypass while 23.7% had sleeve gastrectomy. Baseline mean weight and BMI were 114.4±27.4 kg and 42.5±10.5 kg/m² respectively. Mean weight loss of 26% was achieved at 1 year and sustained over 5 years. Mean HbA1c decreased from 8.3% to 6.0% at 5 years, 18 of 43 (41.9%) patients achieved sustained remission of diabetes with 6 (14.0%) having DM remission.

Table 1. Characteristics of Subjects at Baseline and Over 5-Year Follow-Up.

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Pre-surgery</th>
<th>12 months</th>
<th>24 months</th>
<th>36 months</th>
<th>48 months</th>
<th>60 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>22 (37%)</td>
<td>18 (31%)</td>
<td>13 (24%)</td>
<td>11 (24%)</td>
<td>10 (23%)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>37 (63%)</td>
<td>29 (49%)</td>
<td>31 (56%)</td>
<td>32 (66%)</td>
<td>32 (67%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>43.0±9.5</td>
<td>41.9±9.5</td>
<td>42.0±9.5</td>
<td>42.0±9.5</td>
<td>42.0±9.5</td>
<td>42.0±9.5</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Chinese</td>
<td>24 (40.7%)</td>
<td>22 (37%)</td>
<td>20 (35.8%)</td>
<td>19 (41.3%)</td>
<td>20 (42.6%)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>37 (62.7%)</td>
<td>35 (58.4%)</td>
<td>32 (57.1%)</td>
<td>33 (69.6%)</td>
<td>32 (67.3%)</td>
</tr>
<tr>
<td>Diabetes mellitus duration (months)</td>
<td>82.1±48.3</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Types of surgery</td>
<td>Sleeve gastrectomy</td>
<td>1 (23.7%)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Minip gastric bypass</td>
<td>1 (23.7%)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Roux-en-y gastric bypass</td>
<td>28 (47.5%)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>114.4±27.4</td>
<td>84.9±20.5*</td>
<td>84.5±21.0*</td>
<td>87.5±23.0*</td>
<td>83.1±19.8*</td>
<td>83.2±21.5*</td>
</tr>
<tr>
<td>Body Mass Index (BMI)</td>
<td>42.5±10.5</td>
<td>31.9±8.3*</td>
<td>31.3±7.4*</td>
<td>32.5±8.2*</td>
<td>31.3±8.0*6</td>
<td>32.0±8.67*</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>127.0±14.6</td>
<td>125.6±17.3</td>
<td>125.8±18.2</td>
<td>130.2±17.7</td>
<td>129.7±13.3</td>
<td>135.4±19.2</td>
</tr>
<tr>
<td>Lipid panel (mmol/L)</td>
<td>Cholesterol</td>
<td>7.7±0.5</td>
<td>7.5±1.1</td>
<td>7.9±1.3</td>
<td>8.0±1.0</td>
<td>7.5±0.8</td>
</tr>
<tr>
<td></td>
<td>LDL</td>
<td>4.0±1.3</td>
<td>3.5±0.9*</td>
<td>3.7±0.8*</td>
<td>3.9±0.7*</td>
<td>3.5±0.6*</td>
</tr>
<tr>
<td></td>
<td>Triglyceride</td>
<td>4.56±0.88</td>
<td>2.75±0.81</td>
<td>1.69±0.74</td>
<td>1.05±0.26</td>
<td>1.37±0.32*</td>
</tr>
<tr>
<td></td>
<td>HDL</td>
<td>1.69±0.74</td>
<td>1.15±0.58*</td>
<td>1.30±0.55*</td>
<td>1.42±0.86*</td>
<td>1.41±0.76*</td>
</tr>
<tr>
<td>Lipid-lowering medications</td>
<td>0.81±0.57</td>
<td>0.17±0.47*</td>
<td>0.25±0.44*</td>
<td>0.31±0.59*</td>
<td>0.27±0.49*</td>
<td>0.33±0.51*</td>
</tr>
<tr>
<td>Diabetes remission (n)</td>
<td>NA</td>
<td>28</td>
<td>24</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Continuous data as mean ± SD; categorical data as n (%). * Presence of significant difference when compared to pre-surgery data (p&lt;0.05).</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The mean BMI decreased from 39.4 ± 5.8 kg/m² to 27.1 ± 3.9 kg/m². Patients data, and inflammatory markers were collected pre- and 1, 3, 6, and 12 months group and subclinical hypothyroidism (SCH) group. TSH, FT4, anthropometric interleukin-6 (IL-6), and tumor necrosis factor-α decreased TSH levels correlated significantly with decreased BMI, HOMA-IR, IL-6, and TNF-α, and CRP levels in SCH group, as well as IL-8, TNF-α, and CRP in euthyroid group from baseline by 12 months postoperatively. Moreover, decreased TSH levels correlated significantly with decreased BMI, HOMA-IR, IL-6, and TNF-α at 12 months after LSG.

Conclusion: SCH in severely obese subjects appears to be associated with excess weight, insulin resistance, and elevated inflammatory markers. LSG promotes a decrease of TSH that is significantly greater in patients with SCH, and associated with alleviation of inflammatory status in addition to substantial weight loss and improved insulin resistance after surgery.

Supported By: National Natural Science Foundation of China (81500850, 81707052)

2059-P
After Roux-en-Y Gastric Bypass, Enterohypertrophic Bile Circulation Is Altered and Bile Acid Retention Increased while Bile Acid Homeostasis Remains Normal after Sleeve Gastroctomy
ALEKSANDER EKENS, STEFAN FUGLSANG ESQ., MARKUS LAUGE EKEN, MARIA S. SVANE, JENS J. HOLST, KIRSTINE N. BOJSEN-MOLLER, STEN MADS-BAG, SR., JAN L. MAASSEN, DARSTEN DIRKSEN, HVIDOVRE, COPENHAGEN, DENMARK

Introduction: Elevated bile acid (BA) concentrations have been suggested to partly drive metabolic improvements after bariatric surgery but the mecha

Materials and Methods: 15 RYGB, 10 SG and 15 gender, age and BMI matched controls (C) underwent a combined cholecystectomy and fatty test-meal with frequent blood sampling, for concomitant visualization of radionabeled bile and food markers in the GI tract. BA retention was esti

Results: Prior to meal intake, gallbladder filling was lower (mean ± SEM: RYGB 233 ± 4, SG 39 ± 4, C 36 ± 5, RYGB vs. C p = 0.04) and more bile marker had passed passively into the small intestine in RYGB but not SG (RYGB 48 ± 6, SG 21 ± 5, C 20 ± 8, RYGB vs. C p < 0.01). Postprandial gallbladder emptying was complete in all groups. Gastric retention of foods was negligible in RYGB and lower in SG at 10 min after meal intake RYGB 12% ± 2, SG 59 ± 7, C 90 ± 4, RYGB vs. C p<0.01, SG vs. C p < 0.01) resulting in instant mixing of food with bile in RYGB and accelerated mixing in SG (RYGB 79 ± 3, SG 35 ± 8, C 8 ± 4, RYGB vs. C p < 0.01, SG vs. C p < 0.01). BA-retention over 7 days was only increased in RYGB (RYGB 54 ± 6, SG 34 ± 4, C 33 ± 5, RYGB vs. C p = 0.02). Peak S-cholecystokinin (CCK) was comparably increased in RYG and SG (RYGB 13 pmol/l ± 3, SG 15 ± 3, C 6 ± 1, RYGB vs. C p = 0.03, SG vs. C p = 0.01). Conclusion: After RYGB, enteric BA appearance is altered (more hepatic less gallbladder derived) and food is instantly mixed with bile due to negligible retention of foods in the gastric pouch. BA retention is increased. In contrast, BA appearance and retention remains normal after SG, although gastric emptying is accelerated. The metabolic impact of the changes in BA circulation after RYG needs further evaluation.

Supported By: Novo Nordisk Foundation; Amager and Hvidovre Research Foundation

2060-P
Thyroid Function Improved after Laparoscopic Sleeve Gastroctomy in Severe Obesity and Related to Inflammatory Changes
CUILING ZHU, FANGYUN MEI, JINGYING GAO, XINGCHUN WANG, LIANG LI, LIHESHENG LU, DONGLEI ZHOU, SHEN QU, SHEN QI, HUISHENG, SHEN GU, SHANGHAI, CHINA

Objective: Obesity, a state of chronic low grade inflammation, has been reported to be associated with significant alterations of thyroid function. The purpose of this study is to evaluate the effect of laparoscopic sleeve gastroctomy (LSG) on thyroid function and its relation with inflammatory changes in severely obese patients.

Methods: We performed a retrospective observational study of 128 severely obese patients (61.7% female; age 31.8 ± 10.0 years, BMI 39.4 ± 5.8 kg/m²) divided into the following groups: euthyroid group (all P<0.05). After surgery, TSH levels significantly decreased at 1, 3, 6, and 12 months regardless of thyroid function, which presented more apparent in SCH group. Additionally, we observed marked reduction of IL-6, IL-8, TNF-α, and CRP levels in SCH group, as well as IL-8, TNF-α, and CRP in euthyroid group from baseline by 12 months postoperatively. Moreover, decreased TSH levels correlated significantly with decreased BMI, HOMA-IR, IL-6, and TNF-α at 12 months after LSG.

Conclusion: SCH in severely obese subjects appears to be associated with excess weight, insulin resistance, and elevated inflammatory markers. LSG promotes a decrease of TSH that is significantly greater in patients with SCH, and associated with alleviation of inflammatory status in addition to substantial weight loss and improved insulin resistance after surgery.

Supported By: Shanghai Natural Science Foundation

2061-P
Chemerin and Tissue Inhibitor of Metalloproteinases 2, a Potential Link to Nonalcoholic Fatty Liver Changes in Metabolic Syndrome
SADIA FATIMA, KARACHI, PAKISTAN

Metabolic syndrome (MetS) in Pakistan affects 18-46% individuals. Over nutrition and sedentary behavior acts as a trigger, yet in many instances nor

Supported By: ADA-Supported Research

2062-P
Significant Bone Loss in Obese Patients with Acanthosis Nigerians after LSG—One-Year Follow-Up Study
YOU YANG ZHAO, ZHAN HUI ZHUANG, CUOLIN ZHU, SIQI SUN, YING YIN, RAN CUI, HUI SHENG, SHEN GU, SHANGHAI, CHINA

The aim of the study was to investigate the longitudinal bone mineral density(BMD) and bone metabolic related markers changes in obese patients with acanthosis nigricans (AN) and without AN(OB) after Laparoscopic Sleeve Gastroctomy (LSG). 41 obese patients (AN group:n=29, OB group:n=12) were recruited in this study. Areal BMD (bBMD) and lumbar spine volumetric BMD (vBMD) were measured by dual-energy X-ray absorptiometry (DXA) and quantitative computed tomography (QCT). Insulin and markers of bone metabolism including 25-OH-D, calcium, intact parathyroid hormone (iPTH), osteocalcin (OC), and type I collagen cross-linked C-terminal telopeptide (CTX) were assessed; Insulin area under the curve (AUCins) and HOMA-IR were computed. Results showed that the AN group had a higher fasting serum insulin (42.80 ± 28.52 vs. 22.55 ± 8.34mg/l, p=0.006), AUCins (522.42 ± 280.32 vs. 263.87 ± 195.75mg/l, p=0.008) and BMI (40.6 ± 5.1 vs. 36.7 ± 4.1kg/m², p<0.01), pelvic aBMD (-6.48%, p<0.001) and femoral neck aBMD (-6.7%, p=0.045) after LSG compared with baseline, whereas no detectable BMD changes in the OB group. CTX and OC increased in both AN (97.69%, 78.65%, respectively) and OB (115.21%, 62.28%, respectively) groups; No significant alteration of 25-OH-D, serum calcium, or iPTH was observed.

In conclusion, Insulin resistance was improved, and bone turnover was activated one year after LSG in both groups, but the bone loss was more likely to occur in the obese patients with acanthosis nigricans.

Supported By: Shanghai Natural Science Foundation

A541
2064-P

Visceral and Ectopic Fat Expansion and the Risk of Incident Type 2 Diabetes Mellitus
IAN J. NEELAN, COBY AYERS, KERSHAW V. PATEL, PARAG H. JOSHI, DARREN K. MCGUIRE, SCOTT M. GRUNDY, ANANDI REHATGI, GLOIRA L. VEGA, Dallas, TX

Background: Excess visceral adipose tissue (VAT) is associated with an increased risk of prediabetes and type 2 diabetes (T2D) independent of body mass index (BMI). Whether expansion of VAT or other fat depots is associated with diabetes risk independent of weight gain is not fully known.

Methods: Among participants without prevalent diabetes or cardiovascular disease enrolled in the Dallas Heart Study, we measured body fat distribution by dual energy x-ray absorptiometry and biomarkers of glycaemia at baseline (2000-2002) and repeated 7 years later. The incidence of prediabetes and T2D per ADA definitions were assessed at follow-up.

Results: The study included 1681 participants (mean age 44, 58% women, 45% black, 39% obese) with median weight gain of 3.0 (-1.1 to 7.2) kg. Eight percent of participants developed T2D and, among those with normal fasting glucose at baseline (n=1551), 36% developed prediabetes or T2D. Changes in fat depots are shown in the Table. VAT and SAT gain were associated with incident T2D and with prediabetes or T2D independent of traditional risk factors, baseline BMI, change in BMI, and baseline fat depot (Table). Increasing lower body fat was not associated with incident diabetes.

Conclusions: Expansion of VAT and SAT are both associated with incident T2D independent of weight gain. Abdominal adiposity may be a modifiable target for diabetes prevention even in the absence of generalised weight loss.

Table

<table>
<thead>
<tr>
<th>Fat Depot</th>
<th>Change in Fat Depot</th>
<th>Incident T2D (OR, 95% CI)*</th>
<th>Incident Prediabetes or T2D (OR, 95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAT</td>
<td>Median (IQR) 0.11±0.06 kg</td>
<td>1.90 (1.19-3.06)</td>
<td>1.84 (1.11-2.99)</td>
</tr>
<tr>
<td>Aorta</td>
<td>Median (IQR) 0.28±0.54 kg</td>
<td>1.78 (1.27-2.52)</td>
<td>1.79 (1.34-2.41)</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>Median (IQR) 0.73±0.11 kg</td>
<td>1.90 (1.17-3.06)</td>
<td>1.87 (1.16-2.75)</td>
</tr>
</tbody>
</table>

Notes:
- *Adjusted for age, sex, race, hypertension, smoking, physical activity, family history of diabetes, metabolic syndrome and obesity.
- VAT: visceral adipose tissue; Aorta: aortic adipose tissue; Subcutaneous: subcutaneous adipose tissue

2065-P

BMI Z-Score Trajectories in Youth with T1D—An International Comparison
MENGDI WU, HELEN PHELAN, ANKE SCHWANDT, DAVID M. MAAHS, NICOLE PRINZ, MARIA E. CRAIG, PETER KROSCHWALD, MENGDI WU, HELEN PHELAN, ANKE SCHWANDT, NICOLE C. FOSTER, JENNY JANG YEL SHIN, CHINA

Purpose: To investigate the alteration of body mass index (BMI) z-scores trajectories in youth with type 1 diabetes (T1D) in the T1D ExchangeProspective Follow-up (T1DX) registry in the U.S. compared to TID1 registry in Germany, Austria and Canada.

Methods: Longitudinal data from 11,513 participants between ages 8-17 years with T1D duration ≥3 years and ≥5 aggregated body mass index (BMI) values (ADDN: N=1073, 46% female, mean HbA1c 8.3%; DPV: N=8722, 46% female, mean HbA1c 7.8%; T1DX: N=1718, 45% female, mean HbA1c 8.6%) were analyzed. Participants diagnosed with celiac and/or thyroid disease were excluded. Latent class growth modeling by Nagin was used to identify subgroups following similar BMI z-score trajectories. Five distinct trajectories were identified in ADDN and T1DX participants, and six in DPV (Figure).

Results: Overall, obese participants in T1DX had a lower rate of BMI gain and were less likely to be hypertensive and current drinkers and more likely to be non-smokers than those with the lowest BMI (p<0.001). Patients with the highest tertile of BMI were more likely to be hypertensive and current drinkers and less likely to have regular exercise than those with the lowest BMI (p<0.001). Patients with the highest tertile of BMI were less likely to be involved in diabetes care (p<0.001).

Conclusions: Obese youth with T1D are more likely to have lower BMI z-scores trajectories and are less likely to be involved in diabetes care.

2066-P

Lipid Accumulation Product and Sarcopenia in Korean Patients with Type 2 Diabetes
JANG YEL SHIN, Wonyu, Republic of Korea

Purpose: To investigate the association between Lipid Accumulation Product (LAP) and sarcopenia in patients with type 2 diabetes.

Methods: Total of 481 subjects with type 2 diabetes were enrolled. LAP was estimated as follows: (waist circumference [WC]-65) X (triglycerides [TG] in men and [WC-58] X [TG] in women). Appendicular skeletal muscle mass (ASM) was measured using dual energy X-ray absorptiometry (DEXA). Sarcopenia was defined as follows: ASM/ BMI<0.789 in men and <0.521 in women. Patients with the highest tertile of LAP were more likely to be hypertensive and current drinkers and less likely to have regular exercise than those with the lowest LAP. They had higher values of BMI, systolic and diastolic blood pressure (BP), total cholesterol, HOMA-IR, and liver enzymes and lower values of age, HDL, and vitamin D3 (vitD3). Sarcopenic subjects gradually increased with increasing tertiles of LAP (p<0.05).

Results: Total of 481 subjects with type 2 diabetes were enrolled. LAP was estimated as follows: (waist circumference [WC]-65) X (triglycerides [TG] in men and [WC-58] X [TG] in women). Appendicular skeletal muscle mass (ASM) was measured using dual energy X-ray absorptiometry (DEXA). Sarcopenia was defined as follows: ASM/ BMI<0.789 in men and <0.521 in women. Patients with the highest tertile of LAP were more likely to be hypertensive and current drinkers and less likely to have regular exercise than those with the lowest LAP. They had higher values of BMI, systolic and diastolic blood pressure (BP), total cholesterol, HOMA-IR, and liver enzymes and lower values of age, HDL, and vitamin D3 (vitD3). Sarcopenic subjects gradually increased with increasing tertiles of LAP (p<0.05).

Conclusions: LAP is associated with sarcopenia in patients with type 2 diabetes independent of age, gender, hypertension, current drinking, regular exercise, total cholesterol, HDL, HOMA-IR, CRP, vitD3, and liver enzymes. Further studies are required to investigate a causal relationship between LAP and sarcopenia.

Supported By: The Leona M. and Harry B. Helmsley Charitable Trust; German Center for Diabetes Research; German Diabetes Association; European Foundation for the Study of Diabetes
baseline, 3, 6 and 12 months after LSG (abbreviated as 3M/6M/12M Post-LSG) were recorded. Serum BMP4 levels were measured by enzyme-linked immunosorbent assay. In females, BMD was significantly decreased at right hip at 3M/6M/12M Post-LSG, femoral neck at 6M/12M Post-LSG and L1-L4 at 6M Post-LSG (all P<0.05). In males, BMD was not significantly changed (all P>0.05). Intriguingly, serum BMP4 levels were reduced slightly at 3M Post-LSG (P=0.463), and significantly at 6M Post-LSG (from 75.5±16.54pg/ml to 65.4±10.51pg/ml, P=0.048) in females, while unchanged in males (all P>0.05). In all subjects, free calcium but not total calcium was increased at 12M Post-LSG (P=0.028). Vitamin D and 25(OH)VD were increased in males at 12M Post-LSG (all P<0.05). Osteocalcin was increased in males at 3M/6M Post-LSG and in females at 3M/6M/12M Post-LSG (all P<0.05).

In conclusion, the change of BMD differs between genders after LSG, significantly decreased in females while unchanged in males. Moreover, the decreased BMP4 levels may partly account for the diminished BMD in Chinese female obese subjects after LSG.

2068-P
Impact of Laparoscopic Sleeve Gastroectomy on Thyroid Function Profiles in Chinese Euthyroid Obese Patients
LIANG LI, XINGSCHUN WANG, JINGYANG GAO, SHEN QIU, Shanghai, China

There exists close relationship between thyroid function and obesity. Laparoscopic sleeve gastroectomy (LSG) is an effective bariatric surgery in weight loss and obesity-associated comorbidities. However, only a few studies involve in the alteration of thyroid hormones after LSG with inconsistent results. This study aimed to investigate the impact of LSG on thyroid function profiles in Chinese euthyroid obese subjects. A retrospective study was performed of prospectively collected data in 36 obese patients (17 males and 19 females) who underwent LSG. Thyroid function profiles (T4, T4, TT3, TT4 and TSH, all within normal reference ranges), anthropometric data, and glucose-lipid metabolic parameters were recorded at baseline, 3 and 6 months after LSG (abbreviated as 3M/6M Post-LSG). Correlations between TSH with other parameters were evaluated. In all individuals, BMI was dramatically decreased at 3M/6M Post-LSG accompanied by decreased fasting blood glucose, fasting insulin, fasting C-peptide, triglyceride and increased HDL-C (P<0.01 or P<0.05). T3, T4 and TT3 without TT4 levels were gradually declined from baseline to 6M Post-LSG (P=0.01 or P<0.05, with slight changes in numerical values and still within their normal reference ranges). TSH levels remained unchanged at 3M/6M Post-LSG compared with baseline. In females, the TSH decrease (ATSIII) was positively correlated with BMI decrease (rBMI, P<0.05), percentage of total weight loss (%TWL, P<0.01), and percentage of excess weight loss (%EWL, P=0.051), approximately significant at 6M Post-LSG, while no correlation was observed in males.

In summary, we speculate that euthyroid obese subjects are adept at preserving their thyroid function homeostasis despite of morbid obesity at baseline as well as dramatic weight loss and significant improvement of glucose-lipid metabolism after LSG. In addition, %BMI/%TWL/%EWL may be the predictor of improved TSH levels after LSG in female but not male obese patients.

2069-P
Attitudes Regarding Technology and Weight Loss in Patients with Diabetes and Prediabetes in a Military Health System
ALEXIS BEAUVIS, JANA L. WARDIAN, TOM J. SAUERWEIN, San Antonio, TX

Background: Military dependents and veterans have obesity, prediabetes and diabetes. This study examines the attitudes of patients with type 2 diabetes or prediabetes regarding weight loss and the use of technology in weight management.

Method: A survey was distributed to 3 primary care clinics and a diabetes specialty care clinic in the San Antonio Military Health System (SAMHS) over a two week period in February 2017. Demographics included age, sex, and presence of medical diagnoses including prediabetes and diabetes. Access to and attitudes regarding multiple types of personal technology were assessed. Data analysis was completed using SPSS version 22.

Results: There were 424 surveys collected. Prediabetes was self-reported by 25 (6.6%) respondents and 151 (39.6%) respondents self-reported a diabetes diagnosis. Interest in weight loss was high for patients with prediabetes (100%) and diabetes (73.5%); of those with diabetes that also self-identified as obese, 50 (96.6%) were interested in losing weight. Patients with prediabetes and diabetes were interested in using fitness trackers (65.5%), online videos (57.1%), receiving text messages (53.9%), fitness apps (53.3%), and the existing patient online portal (52.1%). Access to technology was high; many patients owned a personal computer or tablet (76.6%), used text messaging (75%), or owned a smart phone (64.5%). A majority (59.7%) believed technology was helpful for weight loss, but relatively few had used technology in past weight loss efforts (32.4%).

Conclusions: This survey showed that SAMHS patients with prediabetes and diabetes have significant interest in weight loss, access to personal technology devices, and interest in using technology to assist with weight loss. These results will be used to augment existing weight management and health interventions for people with prediabetes and diabetes.

2070-P
A Smartphone App-Based Lifestyle Intervention Promotes Weight Loss—Results of a Prospective, Randomized, Controlled Clinical Trial (RCT)
CHERIE LISA VAZ, AKASHKUMAR G. SUTHAR, BOBAK T. POUSHTI, SU M. AYE, KEVIN JON WILLIAMS, HUAQING ZHAO, Philadelphia, PA

Despite widespread use of smartphones and wearables, we have limited evidence that they aid weight loss or lifestyle. Here, we report results of a 6-month RCT of our smartphone app-based lifestyle intervention vs. standard of care (in-person weight management visits vs. 0, 3, and 6 months) in a cohort of overweight or obese subjects.

The app downloads objective data of daily weights from smart scales and physical activity from 3-axis accelerometers. The technology allows peer social networking and remote professional coaching employing behavior modification techniques delivered via group and private messaging, emoticons, shared activity and weight data, shared photographs of meals, and a virtual reward system for behavior modification. Intervention group, n=13, 85% F, age 39.5 ± 3.71 years, initial weight 94.3 ± 3.42 kg, BMI 34.5 ± 1.3 kg/m². Control group: n=15, 86% F, age 45.1 ± 3.31 years, initial weight 92.3 ± 4.37 kg, BMI 33.8 ± 1.05 kg/m² (means ± SE).

We found a clinically and statistically significant weight difference of -4.2 ± 2.0 kg (95% CI -8.9 to -0.2) (p=0.0489) after 6 months of our smartphone app-based lifestyle intervention (prespecified primary outcome, intervention vs. control). In the intervention group, weight change was -7.2 ± 1.8 kg (95% CI -11.1 to -3.3, p = 0.0017); % weight change was -7.9% ± 2.2% (95% CI -12.8 to -3.2, p=0.0031). Weight change significantly associated with median step counts (Pearson’s correlation coefficient r=-0.81, p=0.027), numbers of text messages from each subject (r=-0.83, p=0.0005), and numbers of diet photos shared (r = -0.83 p=0.0005).

Our app-based lifestyle intervention met the prespecified primary outcome of clinically meaningful and statistically significant weight loss at 6 months over control. The strongest correlations with weight loss in the intervention group were physical activity (step counts) and subjects’ engagement in behavior modification coaching (messages and diet photos).

Supported By: Temple University, Obesity Treatment Foundation

2071-P
Endobarrier® in Type 2 Diabetes/Prediabetes with Obstructive Sleep Apnea Study—Preliminary Results
MAHENDER YADAGIRI, FIONA Y. KINNEY, NATALIE ASHMAN, MICHAEL H. LANG, EDWARD ROGEN, MARK ANDERSON, JOHN BLEASDALE, CHRISTOPHER WALTON, MICHAEL A. GREENSTONE, ROBERT E. RYDER, Birmingham, United Kingdom, Hull, United Kingdom

Aims: To assess the extent to which patients with type 2 diabetes or prediabetes, obesity (BMI 30-45kg/m²) and moderate OSA requiring continuous positive airway pressure ventilation (CPAP) are able to discontinue CPAP following weight loss (ISRCTN33788192).

Methods: We assessed Apnoea Hypopnoea Index (AHI), weight and HbA1c before and following Endobarrier (EB). The full study involves 18 patients receiving EB for up to 1 year with 1 year follow-up.

Results: We report here the first 11 patients (9/11 [82%] female, 9/11 [82%] type 2 diabetes, 2/11 [18%] prediabetes, mean ± SD age 52 ± 6.9 years) to reach at least 3 months EB treatment. In 3 months, weight fell by 6.9 ± 3.3kg from 103.7 ± 14.8 to 96.8 ± 14.8 kg (p<0.001), mean BMI by 2.5 ± 1.3kg/m² from 37.1 ± 3.6 to 34.6 ± 3.7kg/m² (p<0.001), mean HbA1c by 0.9±1.3% from 8.0±0.8 to 7.1±0.7% (p<0.05), OSA improvement (Figure). Prior to EB, all 11 patients had AHI in moderate sleep apnoea range (15-29.9 events/hour). Following EB, the AHI of 7/11 (64%) patients fell below the moderate sleep apnoea threshold of 15 events/hour, such that they no longer required CPAP. Of the remaining 4 patients, 1 came off CPAP at 6 months. This study adds to the evidence that Endobarrier is encouraging in that EB has already allowed 9/11(73%) patients to discontinue CPAP in addition to glycaemic and weight benefits. Discontinuing CPAP is beneficial to health services but especially to patients.
Incretin and Cardiovascular Effects of Weight Loss and Remission of Prediabetes
FRANKIE B. STENTZ, ANN AMMONS, Memphis, TN
Since the incretins GLP-1 and GIP have important roles in insulin sensitivity and have been shown to be effective in cardiovascular disease in the treatment of type 2 diabetes, we studied these incretin level changes with weight loss and remission of prediabetes in 24 obese women and men with prediabetes. Our studies have shown that prediabetes subjects on a 6 month HP diet (30% protein, 30% fat, 40% CHO) had 100% remission of prediabetes compared to only 33% on a HC diet (15% protein, 30% fat, 55% CHO). Subjects on the HP diet had increased satiety compared to the HC diet, therefore, we studied HP and HC diet effects on ghrelin levels. Additionally, since cardiovascular risk factors (CVRF) decreased more in the HP than the HC diet, we determined if the B-Type Natriuretic Peptide (BNP) released from the heart was affected by either diet. GLP-1, GIP, Ghrelin, and BNP levels were determined with a Meal Tolerance Test (MTT) at baseline and after 6 mo on HP and HC diets where all food was provided. Two HP-1 and total GIP area under the curves for the HP MTT increased significantly from baseline vs. 6 months (7986±31 vs. 8970±37 pmol/l/min, p=0.001) and (21,350±63 vs. 27,240±72 pmol/min, p=0.001) respectively. The ghrelin decreased significantly from baseline vs. 6 months on the HP MTT (338±21 vs. 78±14 pmol/l/min, p=0.005). BNP decreased significantly from baseline (126±1±70 pmol/l) to 6 months (78±9 pmol/l, p=0.01). HP diet had a significantly greater increase in GLP-1 and GIP than the HC diet. HP ghrelin results demonstrate that HP diet can induce satiety and is more effective than the HC diet. The BNP decrease in both groups demonstrates the improvement in heart tissue with the HP diet having a greater effect than the HC diet. Although weight loss was similar (9.6% in HP vs. 11.3% in HC, p=0.692), this study demonstrates that the HP diet increases GLP-1 and GIP which may be responsible in part for the improved insulin sensitivity, and decreases BNP with greater improvement in CVRF with remission of prediabetes.

Supported By: AD Baskin

Effects of Laparoscopic Sleeve Gastroectomy on Insulin Secretion Patterns in Young Obese Patients with Acanthosis Nigricans
CHUNHUA QIAN, SHEN QI, CUIYING ZHU, JINGYANG GAO, FANGYUN MEI, LE BU, Shanghai, China
Background: Acanthosis nigricans (AN) is a skin condition commonly often accompanied by insulin resistance and hyperinsulinemia. Patients with AN are prone to diabetes, especially in young obesity. Metformin were often used to treat these patients. However, reports about the effectiveness of LSG surgery on young obese patients with AN are rare.
Objective: The aim of our study was to evaluate the efficacy of LSG surgery on insulin secretion patterns and anthropometric variables for obese patients with AN.
Methods: 30 young obese patients with AN were recruited for this study. Before and at 12 months after the LSG surgery, BMI and blood samples were collected. DSTT were used to evaluate the insulin level and its rhythm of secretion. AN extent and AN texture were determined according to the scale developed and validated.
Results: For these patients, BMI decreased from 40.9±4.93 kg/m² to 27.2±4.13 kg/m² at 12 months after surgery. Along with weight loss, triacylglycerides and total cholesterol decreased significantly, and high-density lipoprotein cholesterol (HDL-C) increased significantly as of 12 months after surgery. But the change of low-density lipoprotein cholesterol (LDL-C) is not obvious. A significant decrease in insulin resistant (HOMA-IR) was observed. The insulin release curves showed hyperinsulinemia and abnormal rhythm of secretion before surgery. At 12 months after the fasting, 2h post-prandial insulin levels and the rhythm of insulin secretion were restored to normal level. But the insulin levels at 30min and 60min were higher than before surgery. The extent of AN for most patients were improved. Only 23.4% patients still were severe (vs. 59.3% before surgery). More than 50% patients were remission.
Conclusion: In this study LSG in obesity patients with AN, we found significant improvements in weight, dyslipidemia, hyperinsulinemia and AN extent. LSG will be a new effective therapeutic approach for young obesity patients with AN.
Supported By: National Natural Science Foundation of China (NSFC81500850); Fundamental Research Funds for the Central Universities (1501219107)

Sleep Quality Is Associated with Obesity in Patients with Type 2 Diabetes
TOMOHIRO HIROYA, TOMOAKI MORIOKA, KIYOHARU YODA, NODAIKO TOU, NODAIKO YUKI HAYASHI, SADIRI MARUJO, MASAFUMI KURAJOH, SHINSUKU YAMADA, YUKI HAYASHI, SAORI MARUO, MASAFUMI KURAJOH, SHINSUKE YAMADA, TETSUO SHOJI, MASANORI EMOTO, MASAKI INABA, Osaka, Japan
Insufficient sleep has been recognized to underlie the epidemic of obesity, type 2 diabetes, hypertension, and cardiovascular diseases. Recent evidence indicates that, not only short sleep duration, but also poor sleep quality is associated with obesity, type 2 diabetes, and metabolic syndrome. However, most of the prior studies evaluated sleep quality subjectively by using a questionnaire. In this study, we objectively evaluated sleep quality and investigated its association with obesity in patients with type 2 diabetes. We included 182 patients with type 2 diabetes, of which 113 had obesity (BMI ≥ 25kg/m²). Objective sleep architecture was measured using single-channel electroencephalography, and slow-wave sleep (SWS) was evaluated as a marker of deep sleep. We also measured apnea-hypopnea index (AHI), and nocturnal blood pressure (BP) by 24-h ambulatory BP monitoring. In a total population, the mean value for age was 58 years, duration of diabetes was 12 years, BMI was 27.8 kg/m², HbA1c was 8.5%, AHI was 15, total sleep time was 345 min, and SWS was 9.8 min. Subjects with obesity (mean BMI 31.2 kg/m²) were younger (56 vs. 62 years) and had higher AHI (18.3 vs. 9.5) than those without obesity (mean BMI 22.2 kg/m²). Neither total sleep time nor SWS was significantly different between the groups. In unchanged analyses, BMI was significantly correlated with AHI, but not with SWS or total sleep time. Multivariate analysis revealed that AHI (β = 0.423, p < 0.001) was positively, while SWS (β = −0.146, p = 0.042), age, and male sex were negatively associated with BMI, after further adjustment for duration of diabetes, nocturnal systolic BP, serum creatinine, and HbA1c. On the other hand, no significant association was found between total sleep time and BMI. In conclusion, SWS is inversely associated with BMI, independently of AHI and other covariates, in patients with type 2 diabetes. This study indicates an adverse relationship between poor sleep quality and obesity, independent of sleep apnea, in patients with type 2 diabetes.

Increased Bile Acids and FGF-19 after Sleeve Gastroectomy and Roux-en-Y Gastric Bypass Correlate with Improvement in Type 2 Diabetes in a Randomized Trial
RINIKI MURPHY, REZA NEMATI, DECH DOKPUANG, JUN LIU, Auckland, New Zeal-
Background: Sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB), are both effective bariatric procedures to treat type 2 diabetes (T2DM) and obesity. The contribution of changes in bile acids (BAs) and fibroblast growth factor19 (FGF-19) to such metabolic improvements is unclear.
Methods: We examined associations between changes in BAs, FGF-19 (fasting and prandial), with changes in body weight, glycemia and other metabolic variables in 61 obese patients with T2DM before and one year after randomisation to SG or RYGB.
Results: Weight loss and diabetes remission (defined by HbA1c <39mmol/mol [<5.7%] in absence of glucose lowering therapy) after RYGB and SG was similar (mean weight loss -29kg vs. -31kg, p=0.50; diabetes remission proportion 37.5% vs. 34%, p=0.10). Greater increments in fasting and prandial levels of total, secondary and unconjugated BAs were seen after RYGB than SG. Fasting and prandial increases in total (n=0.3, p=0.01; n=0.2, p=0.04), secondary (n=0.3, p<0.01; n=0.4, p=0.01) and unconjugated BA (n=0.3, p=0.01; n=0.4, p=0.01)
p=0.01; r=0.4, p<0.01) correlated with decreases in HbA1c, but not weight. Changes in 12×OH/non 12x-OH were positively associated with prandial glucose increments (n=0.2, r=0.03), HbA1c (n=0.3, p=0.01) and negatively associated with changes in insulinogenic index (n=0.3, p=0.01). Only changes in prandial FGF-19 were negatively associated with HbA1c (n=0.4, p<0.01) and visceral fat (r=0.3, p=0.04).

Conclusions/Interpretation: The modest association between increases in secondary, unconjugated BAs and improvements in HbA1c, but (not weight) achieved after both RYGB and SG suggest augmentation of BA signalling as one potential strategy for controlling T2DM through weight independent means.

Supported By: Maurice Wilkins Centre

2076-P A Systems Approach to ER Stress Pathway Dynamics Reveals the Impact of Freeze-Dried Broccoli Extract to Mitigate Inflammation in Human Adipocytes through the Mevalonate Pathway
ALICE MURPHY, SAHAR AZHARIAN, GYANENDRA TRIPATHI, GUY BARKER, MICHAEL J. CHAPPELL, PHILIP G. MCTERNAN, Coventry; United Kingdom, London, United Kingdom, Nottingham, United Kingdom

Background: Delivery of nutrient excess in obesity causes endoplasmic reticulum (ER) stress within adipose tissue; this activates the unfolded protein response (UPR) and contributes to type 2 diabetes mellitus (T2DM) risk. This study aimed to utilise freeze-dried broccoli extract (BE) as a nutrient to mitigate such cellular damage in human adipocytes, and create a mathematical model to understand pathway dynamics.

Methods: Differentiated human adipocytes (Chub-S7; n=6) were treated with BE (10ng/ml) alone or combined with tunicamycin (Tun; 750ng/ml), an inducer of ER stress. UPR proteins (BiP, PERK, P-PERK, eIF2α, P-eIF2α) were measured (16 time points, 3h-72h) using Western Blot and transcriptomics. Mass action kinetics was used to create ordinary differential equations (ODEs) to model the UPR for predictive analysis.

Results: Tun increased UPR proteins 9.5 fold (P<0.05), whilst BE+Tun reduced ER stress proteins by 84% (P<0.05). Transcriptomic analysis highlighted significant changes in the mevalonate pathway with BE (P<0.05), whilst time series data identified oscillatory behaviour of UPR proteins. Finally, modelling pathway dynamics, time-series analysis improved the error between model output and experimental data by 23%, yielding a new enhanced qualitative model.

Conclusion: BE acts to alleviate ER stress in human adipocytes by reducing the UPR through the mevalonate pathway. Furthermore, modelling pathway dynamics using experimental data may provide insight into predicting nutrient capabilities to reduce inflammation.

Supported By: Engineering and Physical Sciences Research Council

2077-P Altered Brain Resting-State Functional Connectivity in Obese Patients Is Associated with Plasma Levels of Leptin
FRANCENTONIO DEVITO, ANNA FERRULLI, LAURA ZAPPAROLI, ROLANDO BONANDRINI, LUCA MARIA SCOFDENZA, GIUSEPPE BANFI, LIVIO LUZI, ERALDO PAULESI, Milan, Italy, San Donato Milanese, Italy

There is growing evidence for the role of the insular cortex in various types of cravings, including food craving. Here, we used resting-state functional brain connectivity (FBC) to explore system-level dysfunctions in the brain of obese (OB) individuals and their correlations with the leptin levels. We first used hierarchical clustering to identify the brain regions whose altered functioning was consistently reported by neuroimaging studies on food perception in OB subjects. We found that a cluster centred in left anterior insula and overlaying frontal operculum (AI/TO) was specifically associated with hyper-responsivity in OB. This cluster was then used as a seed for a seed-based FBC analysis in 10 OB and 11 normal weight controls associated with hyper-responsivity in OB. This cluster was then used as a seed for a seed-based FBC analysis in 10 OB and 11 normal weight controls matched for sex, age and education. The analysis implied the calculation of the functional correlations of each brain voxel with the seed along the matched for sex, age and education. The analysis implied the calculation of the functional correlations of each brain voxel with the seed along the matched for sex, age and education. The analysis implied the calculation of the functional correlations of each brain voxel with the seed along the matched for sex, age and education. The analysis implied the calculation of the functional correlations of each brain voxel with the seed along the AI/TO and key regions of the reward system, such as the left medial orbitofrontal cortex (OFc), in addition to the bilateral parahippocampal gyrus and the posterior cingulate gyrus; conversely, they exhibited hypo-connectivity between the seed and the left dorsolateral prefrontal cortex, a key region involved in inhibitory control (all $p<0.05$ corrected for multiple comparisons). Finally, we found a substantial trend for a negative correlation between AI/TO-FHC hyper-connectivity and plasma levels of leptin ($r=-0.1$, $p<0.02$). Our results provide evidence for an imbalance between reward and inhibitory control systems in OB patients, which might be worsened by an altered response to food intake regulatory hormones (e.g., anorexigenic leptin), thus driving the overeating behavior. Moreover, our results suggest that the left AI could be a suitable target for drugs or neuro-modulatory treatment to recalibrate the FBC of a network involved in food intake, reward and cognitive control.

Supported By: Italian Ministry of Health

2078-P Lower Ectopic Fat Accumulation in Obese Women May Help Explain Sex Differences in the Magnitude of Insulin Resistance
JENNA B. GILLEN, BENJAMIN J. RYAN, RACHEL A. GIUSDA-RYAN, ALUSON LUDZKI, THOMAS L. CHENEVERT, JEFFREY E. HOROWITZ, Ann Arbor, MI

Accumulating evidence suggests obese women maintain higher insulin sensitivity than obese men, but factors underlying this sex difference in insulin resistance remain unclear. We recently developed a semi-automated method for quantifying visceral and hepatic fat using advanced chemical shift-encoded magnetic resonance imaging (MRI). Using this method, we explored whether sex differences in ectopic fat accumulation may contribute to differences in insulin resistance. Twenty-one obese women (32 ± 6 years, 34.5 ± 3.1 kg/m², 43.1 ± 5.5 kg fat mass (FM)) and a well-matched cohort of fifteen obese men (29 ± 6 years, 34.5 ± 3.3 kg/m², 42.0 ± 7.8 kg FM) underwent an MRI scan during which 5mm axial slices were acquired from the abdominal region. Using 3D Slicer software, visceral fat area was quantified on three axial slices from the L2-L3 vertebral region and averaged. Hepatic fat was quantified as the average percentage fat from three axial slices of the liver. On a separate day, subjects underwent a hyperinsulinemic-euglycemic clamp to quantify insulin sensitivity. Compared with men, women had lower hepatic (4.2 ± 5.5 vs. 13.1 ± 9.7%, p<0.001) and visceral (114 ± 49 vs. 201 ± 87 cm², p<0.001) fat, which corresponded with higher insulin sensitivity (Glucose infusion rate during clamp [GIR] 514 ± 330 vs. 263 ± 134 umol/kgF/M/30s/min, p<0.05). To further examine the relationship between ectopic lipid accumulation and insulin resistance, we stratified subjects into tertiles by hepatic fat content (n=12 per group). Interestingly, nearly all subjects in the lowest tertile for hepatic fat (11.1 ± 0.6%) were women, and when compared to the highest hepatic fat tertile (17.7 ± 8.2%), they also had lower visceral fat (101 ± 61 vs. 214 ± 83 cm², p<0.001) and importantly, were also more insulin sensitive (GIR: 626 ± 350 vs. 279 ± 238 umol/kgF/M/SSI/min, p<0.05). Our findings suggest lower ectopic fat deposition may help explain the lower degree of insulin resistance in obese women compared with men.

Supported By: National Institutes of Health (R01DK079786, T2D2X002245, P30DK089503, ULTR004330), Canadian Institutes of Health Research

Collaborative Intensive Lifestyle Weight (Wt) Loss Intervention in Underserved Predominantly African-American (AA) Patients in Chicago
CAROLINE POKU, BETTINA TAHSIN, LEON FOSELEFD, Chicago, IL

Minorities are disproportionately affected by obesity. Intensive lifestyle interventions (ILI) have been shown to result in a moderate amount of clinically significant weight loss (5% BW), less so in minorities. Few ILI are culturally adapted for minorities. A collaborative multidisciplinary team implemented a culturally-tailored ILI using current guidelines in a predominantly AA obese population in a primary care setting. Program consisted of individual and group sessions led by MD, RD, PT, and psychologist meeting for 6 months. After the initial ILI, a 6 month maintenance period of monthly meetings with an intensity every 3rd month of 3 visits/month aimed to prevent weight regain. Program goals were to attain a 5% weight loss in 6 months and prevent weight regain after the intensive phase. 40 English-speaking patients enrolled: median age 52.0 years (41.5, 60.0), 77.5% female, 72% AA, 15% Hispanic with median weight 278.9 lbs (236.0, 324.1) and median BMI 44.7 kg/m² (27.7, 55.1). 60% completed the program with 25% of those achieving at least 5% weight loss in 8 months. Results correlated with attendance (Figure). Of the 25% attaining the initial 5% weight loss, 60% showed continued weight loss in maintenance, notably after intensification periods. In this study, attendance and maintenance intensification appeared to be key to continued loss success.

Supported By: ADA-Supported Research  Integrated Physiology/Obesity

Moderated Poster Discussion

OBESITY—HUMAN

A545
Improved Insulin Sensitivity and Irisin after a Dietary Weight-Lowering Program in Obese, Otherwise Healthy Subjects

ADELA PENESOVA, ZOFIA RADIKOVA, BORIS BAJER, MIROSLAV VLCEK, Bratislava, Slovakia

Recent studies suggest that serum irisin might be a predictor of insulin resistance in obese subjects. The aim of the study was to analyze the effect of lifestyle intervention on insulin sensitivity, irisin, and visfatin concentrations.

Methods: A group of 43 obese patients (13M/30F; 43.0±12.4 years; BMI 31.2±6.3 kg/m²) participated in a weight loss interventional program (NCT02255804) following an 8-week program consisting of hypocaloric diet (-30% energy intake) and physical activity 150 minutes/week. Insulin sensitivity was evaluated according to the homeostasis model assessment of insulin resistance (HOMA-IR) and insulin sensitivity indices according Matsuda and Cederholm were calculated (ISIMat and ISICed). Plasma ALT, AST, irisin, visfatin, and physical fitness were measured.

Results: The average reduction of body weight was 6.8±4.9 kg (0-15 kg; p=0.0006), accompanied with significant reduction of body fat mass (p=0.03), and waist circumference (p=0.01). Insulin sensitivity improved (IR HOMA 2.71±1.90 vs. 1.24±0.83; p=0.01; 2hIns 1.64±4.38 vs. 8.93±5.36 p≤0.001; ISICed 59.1±21.14 vs. 64.7±22.2 p=0.003). Total and LDL cholesterol, as well as triglycerides decreased (p=0.02, p=0.02, p=0.05 resp.). Physical fitness significantly improved after intervention (as measured by VO2 max; 25.1±5.9 vs. 28.0±6.0 ml·kg⁻¹·min⁻¹, p=0.001). Plasma irisin significantly decreased after intervention (233±66 vs. 167±88 ng/mL; P<0.001), while visfatin levels did not changed.

Conclusion: Eight weeks of diet and physical activity intervention program in obese otherwise healthy subjects led to improvement of insulin sensitivity, as well as physical fitness and lowering of plasma irisin levels. Irisin strongly reflects body fat mass, suggesting that the irisin circulating levels are conditioned by adiposity level.

Supported By: APV 15-0228; VEGA 2/0161/16

Influence of Race, Ethnicity, and Behavioral Factors on Childhood Obesity

PRISCILLA AYINE, EMILY P. PARRA, RAMESH B. JEGANATHAN, GEETHA THAN-GIAH, Auburn, AL

Childhood obesity is a public health concern resulting from a variety of reasons. In the United States, approximately 12.7 million children and adolescents are classified as obese. 23.8% of African American children are obese compared with 13.1% of whites between ages 6 to 11 years. In Alabama, 35.5% children are overweight and obese, it is 8th highest ranked in United States. The most common causes of childhood obesity are behavioral, genetic factors, or a combination of both.

In this study we investigated the differences in some of the behavioral factors such as sleeping time, dinner time and television watching time in racial ethnic groups. 24 white/European American (EA) and 30 black/African American (AA) elementary school children aged between 6 to 10 years participated in this study. Height and weight were measured, without shoes and wearing only light clothing. Body mass index (BMI) percentile was calculated using Centers for Disease Control and Prevention growth reference. Parents reported child’s typical weekday bedtime, dinner time and television watching time of their children.

35% of EA children slept later than 8:30 pm during school days compared to 68% of AA children. Only 4% of EA children had late dinner (after 7 pm), whereas 50% of AA children had late dinner during weekdays. 21% of EA children watched television for more than 1 hour in comparison to 79% of AA children every day. Our findings suggest that insufficient sleep, late dinner schedule, and longer television exposure are some of the behavioral factors that contribute to greater percentage of childhood obesity in AA than EA children.

Supported By: Auburn University (to G.T.)
2084-P

Impact of Obesity on Outcomes of Diabetic Ketoacidosis—Results from the National Inpatient Sample

ARWA ELsheikh, ABDULLAH ABDULLAH, ABDUL WAHAB, GEORGE E. EIGBIRE, AMR SALAMA, KRISHNAKUMAR RAJAMANI, Rochester, NY

Introduction: Obesity is associated with better outcomes in patients hospitalized for diabetic ketoacidosis (DKA). The impact of obesity and morbid obesity in DKA is not well studied.

Objective: To estimate the impact of obesity and morbid obesity on in-hospital mortality in patients hospitalized for diabetic ketoacidosis (DKA).

Methods: Data from the National Inpatient Sample (NIS) for the years 2012 to 2014, Health Care Utilization Project were reviewed. Patients with a diagnosis of DKA were included using the relevant ICD 9 codes. The primary outcome measured was in-hospital mortality. The Odds Ratio (OR) adjusted for age, gender, Charlson index and sepsis was calculated for obesity and morbid obesity (BMI 30-40) was not associated with increased mortality.

Results: Among 24 obese patients (BMI 36.5±5.0 kg/m²) with glucose intolerance, normal blood pressure, and no cardiovascular events. Cardiac vagal (HFnu-HR) and sympathetic (LFnu-HR) activity were measured by spectral analysis of heart rate variations during 6 minutes of controlled breathing rate (12 cycles/minute) (Task Force Monitor®). These measurements were performed at fasting and after a standardized breakfast including 75g of carbohydrates. The changes (Δ) between fasting and 2 hours after breakfast were calculated.

Results: At fasting, age correlated positively with LFnu-HR (p=0.02) and negatively with HFnu-HR (p=0.02). There was no significant correlation between autonomic indexes and glycemia and insulinaemia. At fasting, FFA correlated positively with LFnu-HR and LF/HF-HR and negatively with HFnu-HR (p=0.04 and <0.02, respectively) and positively with nitrotyrosine (p=0.01). The correlations of FFA with spectral indexes were not altered after age adjustment, but were no more significant after adjustment for nitrotyrosine. Post-prandially, ΔFFA correlated positively with ΔLFnu-HR and ΔLF/HFnu-HR and negatively with ΔHFnu-HR (p=0.04 to <0.02).

Conclusion: In prediabetic obese patients, FFA (lipotoxicity) play an important role both at fasting and post-prandially in sympathetic activation and vagal depression, probably by increasing oxidative stress. These effects could increase the arrhythmogenic risk.

2085-P

Role of Free Fatty Acids in the Alteration of Cardiovascular Autonomic Activity and Its Postprandial Changes in Obese Patients with Glucose Intolerance

AMEL REZKI, MARINOS FYSEKDIS, CHIHIE SABRINA, ISABELA BANU, EMMANUEL COSSON, PAUL VALENSI, Bondy, France, Bobigny, France

Rationale: Depressed cardiac vagal activity and elevated sympathetic activity have been reported in prediabetic obese patients. In healthy individuals, insulin was shown to acutely induce such changes, and free fatty acids (FFA) to enhance sympathetic activity. This study aimed to examine the relations between glycemia, insulinaemia and plasma FFA with cardiovascular autonomic activity in obese patients with glucose intolerance.

Patients and Methods: We included 24 obese patients (BMI 36.5±5.0 kg/m²) with glucose intolerance, normal blood pressure, and no cardiovascular events. Cardiac vagal (HFnu-HR) and sympathetic (LFnu-HR) activity were measured by spectral analysis of heart rate variations during 6 minutes of controlled breathing rate (12 cycles/minute) (Task Force Monitor®). These measurements were performed at fasting and after a standardised breakfast including 75g of carbohydrates. The changes (Δ) between fasting and 2 hours after breakfast were calculated.

Results: At fasting, age correlated positively with LFnu-HR (p=0.02) and negatively with HFnu-HR (p=0.02). There was no significant correlation between autonomic indexes and glycemia and insulinemia. At fasting, FFA correlated positively with LFnu-HR and LF/HF-HR and negatively with HFnu-HR (p=0.04 and <0.02, respectively) and positively with nitrotyrosine (p=0.01). The correlations of FFA with spectral indexes were not altered after age adjustment, but were no more significant after adjustment for nitrotyrosine. Post-prandially, ΔFFA correlated positively with ΔLFnu-HR and ΔLF/HFnu-HR and negatively with ΔHFnu-HR (p=0.04 to <0.02).

Conclusion: In prediabetic obese patients, FFA (lipotoxicity) play an important role both at fasting and post-prandially in sympathetic activation and vagal depression, probably by increasing oxidative stress. These effects could increase the arrhythmogenic risk.

2086-P

Endobarrier® Gastrointestinal Liner in Obese Subjects with Type 2 Diabetes—Short- and Midterm Effects on Glucose Metabolism

NORBERT J. TIRPOLT, FELIX ABERER, JASMIN URL, PETER N. PFERSCHY, CHRISTOPH HÜGNERAUER, FLORIAN SCHREIBER, ANDREAS EHERER, EVA SVEHLIKOVA, CAREN SOURJU, ANNA M. ÖBERMAYER, VANESSA STADLBÄUER, HARALD SOURJU, Graz, Austria

Background: A 60cm endoscopically implantable, duodenal-jejunal bypass liner (Endobarrier®) has been introduced as a therapeutic option for obese subjects with type 2 diabetes (T2DM). The aim of the study was to explore short- and mid-term metabolic effects in the clamp setting.

Materials and Methods: This open, single-center trial investigated 10 obese, T2DM subjects with suboptimal glycemic control (HbA1c >48mmol/mol). Prior to the implantation of the gastrointestinal liner (baseline), 4 weeks and 9 months (explantation) after, all subjects underwent Dual-energy X-ray absorptiometry (DXA) measurement, assessment of beta cell function and insulin sensitivity by a Bolnia clamp procedure and a mixed-meal tolerance test.

Results: We investigated 10 patients with a mean age of 48±9 years and mean diabetes duration of 7±6 years. Detailed results and changes over the time are given in Table. No device has been removed prematurely.

Conclusion: Treating obese T2DM subjects by an endoluminally implanted Endobarrier® leads to moderate weight reduction with large inter-individual variation. Significant improvements in insulin sensitivity occurred already 4 weeks after the Endobarrier® implantation, which were maintained until the explantation of the device, accompanied by reductions in blood pressure.

Impact of Obesity on Outcomes of Diabetic Ketoacidosis—Results from the National Inpatient Sample

ARWA ELsheikh, ABDULLAH ABDULLAH, ABDUL WAHAB, GEORGE E. EIGBIRE, AMR SALAMA, KRISHNAKUMAR RAJAMANI, Rochester, NY

Introduction: Obesity is associated with better outcomes in patients with myocardial infarction and sepsis among other conditions a phenomena being described as obesity paradox. The impact of obesity and morbid obesity in DKA is not well studied.

Objective: To estimate the impact of obesity and morbid obesity on in-hospital mortality in patients hospitalized for diabetic ketoacidosis (DKA).

Methods: Data from the National Inpatient Sample (NIS) for the years 2012 to 2014, Health Care Utilization Project were reviewed. Patients with a diagnosis of DKA were included using the relevant ICD 9 codes. The primary outcome measured was in-hospital mortality. The Odds Ratio (OR) adjusted for age, gender, Charlson index and sepsis was calculated for obesity and morbid obesity respectively.

Results: A total of 4,468,339 individuals with a diagnosis of DM were reviewed in this retrospective study. 132,362 patients (2.96%), who had a diagnosis of DKA were included. In patients with DKA, obesity (BMI 30-40) was present in 7.63% (5.77%). Morbid obesity was present in 5.29% (4%). Mortality was 1.8% vs. 1.9%, p=0.05 in patients with obesity and (3.5% vs. 1.9%, p<0.001) in patients with morbid obesity. In multiple logistic regression and after adjustment to age, gender, Charlson index and sepsis, morbid obesity was associated with increased OR for mortality: 1.37 (95% CI, 1.18-1.61).

Conclusion: In patients with DKA, morbid obesity was associated with increased mortality. A BMI of 30-40 was not associated with increased mortality. No protective effect of obesity or morbid obesity (obesity paradox) was observed in our study.

Impact of Obesity on Outcomes of Diabetic Ketoacidosis—Results from the National Inpatient Sample

ARWA ELsheikh, ABDULLAH ABDULLAH, ABDUL WAHAB, GEORGE E. EIGBIRE, AMR SALAMA, KRISHNAKUMAR RAJAMANI, Rochester, NY

Introduction: Obesity is associated with better outcomes in patients with myocardial infarction and sepsis among other conditions a phenomena being described as obesity paradox. The impact of obesity and morbid obesity in DKA is not well studied.

Objective: To estimate the impact of obesity and morbid obesity on in-hospital mortality in patients hospitalized for diabetic ketoacidosis (DKA).

Methods: Data from the National Inpatient Sample (NIS) for the years 2012 to 2014, Health Care Utilization Project were reviewed. Patients with a diagnosis of DKA were included using the relevant ICD 9 codes. The primary outcome measured was in-hospital mortality. The Odds Ratio (OR) adjusted for age, gender, Charlson index and sepsis was calculated for obesity and morbid obesity respectively.

Results: A total of 4,468,339 individuals with a diagnosis of DM were reviewed in this retrospective study. 132,362 patients (2.96%), who had a diagnosis of DKA were included. In patients with DKA, obesity (BMI 30-40) was present in 7.63% (5.77%). Morbid obesity was present in 5.29% (4%). Mortality was 1.8% vs. 1.9%, p=0.05 in patients with obesity and (3.5% vs. 1.9%, p<0.001) in patients with morbid obesity. In multiple logistic regression and after adjustment to age, gender, Charlson index and sepsis, morbid obesity was associated with increased OR for mortality: 1.37 (95% CI, 1.18-1.61).

Conclusion: In patients with DKA, morbid obesity was associated with increased mortality. A BMI of 30-40 was not associated with increased mortality. No protective effect of obesity or morbid obesity (obesity paradox) was observed in our study.
Effects of Deep Transcranial Magnetic Stimulation (dTMS) on Anti-Inflammatory Gut Bacterial Species in Obesity

Anna Ferrulli, Marco Tosciano, Michela Adamo, Ileana Terruzzi, Lorenzo Dragio, Livio Luzi, San Donato Milanese, Italy, Milan, Italy

Growing evidence highlights the crucial role of gut microbiota in affecting different aspects of obesity. Potential mechanisms for microbial control over eating behavior include microbiota influence on reward and satiety pathways, neurotransmitters release, and hypothalamic-pituitary-adrenal (HPA) axis modulation. A methodology proved to be effective in modulating orexigenic/anorexigenic pathways and food-reward system in obesity is the dTMS. Considering its assets, we hypothesized a potential role of dTMS in inducing weight loss in obesity also via microbiota composition modulation.

Twenty-two obese subjects (5 M, 17 F; 44.6±2.5 years; BMI 37.5±1.1 kg/m2) were allocated into 3 groups receiving 15 sessions (3 per week for 5 weeks) of high frequency (18 Hz, HF), low frequency (1 Hz, LF) dTMS, or sham stimulation. Fecal samples were collected at baseline and after 5 weeks of treatment. Total bacterial DNA was extracted from fecal samples using the QIAamp DNA Stool Mini Kit (Qiagen, Italy) and analyzed by a metagenomics approach (Ion Personal Genome Machine). After 5 weeks, a weight loss in HF (-3.4±1.0%; p<0.05) was found, associated with a decrease in the abundance of bacterial species with pro-inflammatory properties.

In conclusion, the weight loss, induced by HF dTMS, improves sympathetic activity and gut microbiota composition in obese subjects, mainly promoting bacterial species with anti-inflammatory properties, that are typical of healthy subjects intestinal flora.

Supported By: Italian Ministry of Health

WITHDRAWN
cantly predicted cardiovascular events in CVD patients with T2DM and normal sleep is characterized by increased glycogen stores and reduced glucose turnover by metabolically active tissues, thus it is a state of decreased metabolism. It has been reported that reduced sleep quality is associated with increased insulin-resistance and disrupted metabolism. However, the relationship between energy expenditure during sleep (EEDS) and insulin-resistance (homeostasis model assessment, HOMA-IR) has not been clarified. The aim of this study was to investigate the role of EEDS in the association between sleep quality and insulin resistance. A total of 226 individuals (women 72.1%, mean (SD) age 50.46 (±13.1) years; BMI 33.4 (±8.41) Kg/m²) undergoing the oral glucose tolerance test (OGTT) were also asked to wear a metabolic holter (Armband) for 3-days, to assess their daily energy expenditure. The Armband is capable of measuring energy expenditure every minute, but also the duration and quality of sleep. The EEDS corrected for weight (EEDS/WEIGHT) was lower in patients with insulin resistance, HOMA-IR above 2.5 (p < 0.001). The EEDS/WEIGHT was inversely related to HOMA-IR (r = -0.23; p < 0.001) and directly to the quality of sleep (r = 0.15; p < 0.001). Using a multivariate linear regression, with sleep quality, age, gender, glucose and insulin area under the curve (AUC) and EEDS/WEIGHT as independent variables, the HOMA-IR value was independently and significantly predicted by the insulin AUC (p < 0.001), by gender (p < 0.01, beta = 0.155) and by the EEDS/WEIGHT (p < 0.004, beta = -0.173). EEDS is an independent marker of insulin resistance. The mechanism underlying this correlation may be explained by the state of reduced glucose uptake during sleep, which it is further increased during insulin-resistance conditions, with a consequential reduction in energy production. This finding may provide another explanation to the inverse association between sleep quality and metabolic disorders such as type 2 diabetes and obesity.

2092-P

**The A Body Shape Index and Type 2 Diabetes Are Mutually Independent Predictors of Cardiovascular Events in Patients with Peripheral Artery Disease**

ALEXANDER VONBANK, CHRISTOPHER H. SAELE, CHRISTINE HEINZLE, DANIELA ZANDULIN, BARBARA LARCHER, ARTHUR MADER, ANDREAS LEHREK, AXEL MUENDELEIN, HEINZ DREXEL, Felitickitch, Austria, Berna, Switzerland, Triessen, Liechtenstein, Philadelphia, PA

The A Body Shape index (ABSI) is calculated based on waist circumference, height and BMI and is a validated measure of visceral adiposity. In the general population, the ABSI has been shown to be an independent risk factor for premature mortality. Its power to predict cardiovascular events in patients with peripheral artery disease (PAD) is not known and is addressed in this present study. We prospectively recorded cardiovascular events in 319 patients with sonographically verified PAD over a mean follow-up time of 7.2±2.1 years. At baseline, the ABSI was significantly higher in patients with type 2 diabetes (T2DM) than in those who did not have diabetes (19.5±1.9 vs. 14.0±1.1; p<0.001). Prospectively, the ABSI significantly predicted the incidence of cardiovascular events (n=57) both univariately (standardized HR 1.38 (1.20-1.52); p<0.001) and after adjustment for age, gender, smoking, LDL cholesterol, HDL cholesterol, hypertension and T2DM (standardized adjusted HR 1.17 (1.08-1.29); p=0.010); also T2DM significantly predicted cardiovascular events in this fully adjusted model (adjusted HR 1.48 [1.25-1.74]; p<0.001). We conclude that the ABSI and T2DM are mutually independent of cardiovascular events in patients with PAD.

2093-P

**Effect of Restricted Caloric Intake and Bariatric Surgery on PCSK9 Concentrations in Plasma**

HUSAM BAHNIM, SANAA ABDUYAHEEH, SCOTT MONTE, PARESH DANDONA, Buffalo, NY; Orchard Park, NY; Williamsville, NY

PCSK9 is a major modulator of LDLc through internalization and endosomal degradation of LDL receptor. It has been shown that PCSK9 plasma levels predict CVD risk. Bariatric surgery is known to reduce both LDLc and PCSK9. However, its exact effect on circulating PCSK9 levels has not been fully investigated. We have now investigated the effect of strict caloric restriction and Roux-en-Y bariatric surgery (RYBG) in 15 morbidly obese patients (±8.41) Kg/m² undergoing the oral glucose tolerance test (OGTT) were also asked to wear a metabolic holter (Armband) for 3-days, to assess their daily energy expenditure. The Armband is capable of measuring energy expenditure every minute, but also the duration and quality of sleep. The EEDS corrected for weight (EEDS/WEIGHT) was lower in patients with insulin resistance, HOMA-IR above 2.5 (p < 0.001). The EEDS/WEIGHT was inversely related to HOMA-IR (r = -0.23; p < 0.001) and directly to the quality of sleep (r = 0.15; p < 0.001). Using a multivariate linear regression, with sleep quality, age, gender, glucose and insulin area under the curve (AUC) and EEDS/WEIGHT as independent variables, the HOMA-IR value was independently and significantly predicted by the insulin AUC (p < 0.001), by gender (p < 0.01, beta = 0.155) and by the EEDS/WEIGHT (p < 0.004, beta = -0.173). EEDS is an independent marker of insulin resistance. The mechanism underlying this correlation may be explained by the state of reduced glucose uptake during sleep, which it is further increased during insulin-resistance conditions, with a consequential reduction in energy production. This finding may provide another explanation to the inverse association between sleep quality and metabolic disorders such as type 2 diabetes and obesity.

**2094-P**

**Energy Expenditure during Sleep Is an Independent Marker of Insulin-Resistance—A Cross-Sectional Study of Overweight/Obese Subjects**

DARIO TUCCINARDI, ERNESTO MADDEMOLI, ILARIA CAPASSO, LORENZO RAMPA, ANDREA SOARE, DARIO MAGGI, GIUSEPPE DEFEUDIS, SHADI KYANVASH, ANNA RITA MURAZD, PAOLO POZZILLI, SILVIA MARMIRINI, Rome, Italy

Normal sleep is characterized by increased glycogen stores and reduced glucose turnover by metabolically active tissues, thus it is a state of decreased metabolism. It has been reported that reduced sleep quality is associated with increased insulin-resistance and disrupted metabolism. However, the relationship between energy expenditure during sleep (EEDS) and insulin-resistance (homeostasis model assessment, HOMA-IR) has not been clarified. The aim of this study was to investigate the role of EEDS in the association between sleep quality and insulin resistance. A total of 226 individuals (women 72.1%, mean (SD) age 50.46 (±13.1) years; BMI 33.4 (±8.41) Kg/m²) undergoing the oral glucose tolerance test (OGTT) were also asked to wear a metabolic holter (Armband) for 3-days, to assess their daily energy expenditure. The Armband is capable of measuring energy expenditure every minute, but also the duration and quality of sleep. The EEDS corrected for weight (EEDS/WEIGHT) was lower in patients with insulin resistance, HOMA-IR above 2.5 (p < 0.001). The EEDS/WEIGHT was inversely related to HOMA-IR (r = -0.23; p < 0.001) and directly to the quality of sleep (r = 0.15; p < 0.001). Using a multivariate linear regression, with sleep quality, age, gender, glucose and insulin area under the curve (AUC) and EEDS/WEIGHT as independent variables, the HOMA-IR value was independently and significantly predicted by the insulin AUC (p < 0.001), by gender (p < 0.01, beta = 0.155) and by the EEDS/WEIGHT (p < 0.004, beta = -0.173). EEDS is an independent marker of insulin resistance. The mechanism underlying this correlation may be explained by the state of reduced glucose uptake during sleep, which it is further increased during insulin-resistance conditions, with a consequential reduction in energy production. This finding may provide another explanation to the inverse association between sleep quality and metabolic disorders such as type 2 diabetes and obesity.

**2059-P**

**Impact of the Intragastric Balloon Associated with Diet on the Treatment of Diabetic Patients with Overweight or Grade I Obesity and Its Influence on the Production of Enterohormones**

SILVIA M. REMAIO, MARIA ELIZABETH R. DA SILVA, GABRIEL C. NUNES, LUZ HENRIQUE M. MESTIERI, ROSA F. SANTOS, EDUARDO G. DE MOURA, São Paulo, Brazil

Introduction: Obesity is one of the most important public health problems facing the world today. Intragastric balloon (BIB) is a short term, reversible, minimally invasive method for weight loss. Furthermore, it helps changing eating habits and behavior. It promotes gastric distension, resulting in decreased intake of food, delays gastric emptying and enhances the feeling of satiety. The objective of this study was to evaluate the effects of BIB in patients with type 2 diabetes mellitus (T2DM) and overweight or with grade I obesity, by analyzing the weight loss, body composition, glucose and lipid metabolism, production of enterohormones and quality of life.

Methods: Clinical trial including 40 patients with T2DM and BMI 27-34.9 kg/m², which underwent placement of BIB, kept for 6 months, and follow-up for another 6 months after withdrawn. A standardized meal test diet was carried out at 0 and 6 months. Glucose, insulin, triglycerides, GLP-1 active and total PYY were measured at times 0, 30, 60, 120 and 180 minutes.

Results: The total weight decreased by 15.6 ± 7.23 kg after 6 months of use of BIB, which corresponds to loss of 17.1% of the total weight. After 6 months of follow-up, mean weight loss was maintained at 13.89 kg (15.2%). There was a significant reduction in body fat mass and area of the glucose curve, insulin and triglycerides (p ranged from <0.001 to 0.003). Of the 24 patients (60%) patients with hypertension at baseline, only 3 (7.5%) remained hypertensive after using the BIB. Serum levels of active GLP-1 and total PYY decreased with BIB. The quality of life improved in all domains analyzed (p <0.001 to 0.041), physical functioning, physical function, pain, general health, vitality, social functioning, emotional aspects and mental health.

Conclusion: BIB is effective for weight loss and control of DM2 with quality of life improvement. There is no positive correlation with the production of enterohormones.

**2096-P**

**WITHDRAWN**
First Risk ‑Benefit Data from the Worldwide Endobarrier Registry

ROBERT E. J. RYDER, LYNNNE MUNRO, JESSICA J. MCMASTER, JUSTIN BESSELL, JEANINE M. BASCOME, JANE E. COLLINNS, LILIAN KOW, JACOB CHISHOLM, HARALD SOURIJ, PETER N. PERSCHY, JR., JULIAN P. TEARE, JOHN C. MASON, JAMES P. BYRNE, MELODY C. WYRCS, MELISSA L. OLL, WYN BURBRIDGE, SUSAN P. IRWIN, MAHENDER YADAGIRI, EDWARD FOGDEN, MARK ANDERSON, HARRISON HIDALGO, TERRY FOGDEN, TERRY BURBRIDGE, DONALD PAYNE, DIANA VALENTINE, MAREK BENES, TIM WHITFIELD, ALEXANDRA SIANNI, SATOSHI YAMAMOTO, SUSAN P. IRWIN, MAHENDER YADAGIRI, EDWARD FOGDEN, MARK ANDERSON, HARRISON HIDALGO, TERRY FOGDEN, TERRY BURBRIDGE, DONALD PAYNE, DIANA VALENTINE, MAREK BENES, TIM WHITFIELD, ALEXANDRA SIANNI, SATOSHI YAMAMOTO, and HOUSE OF SCIENTISTS

Introduction: Endobarrier (EB), a novel endoscopic duodenal jejunal liner device for obesity, both with and without diabetes. In view of this, during 2017, an independent, secure, on-line registry was established under the auspices of the Association of British Clinical Diabetologists, for the collection of safety and efficacy data worldwide. As of December 2017, data had been entered on 403 patients, of which 110 (27.3%) were women with a mean age of 58 ± 5 years and 40 (26.6%) were men with a mean age of 62 ± 6 years. Mean BMI was 36 ± 4 and patients received oral medication for the treatment of DM2 (metformin ± DPP-4 ± sulfonylureas ± glitazone). The study duration was one year and HbA1c, fasting glucose, body weight, and body mass index (BMI) were measured at 3, 6, 9 and 12 months. Patients changed their medication to metformin + GLP-1 + SGLT2.

Results: A decrease in HbA1c levels were observed at 3 months (mean HbA1c 12 ± 1), at 8 months (mean HbA1c 9 ± 1), at 9 months (mean HbA1c 8.7 ± 1) and at 12 months (mean HbA1c 7 ± 0.8) (p = 0.030). Fasting glucose also showed a gradual reduction in the follow ‑up tests, namely 185 ± 29mg/dl, 168 ± 22mg/dl, 156 ± 20mg/dl and 145 ± 18mg/dl at 3, 6, 9 and 12 months respectively (p = 0.0045). Similar results were also observed when body weight was measured at 3.6.9 and 12 months (125 ± 18 kg, 108 ± 14 kg, 100 ± 8 kg and 98 ± 8 kg respectively) (p = 0.042). Changes in BMI were also observed with a mean BMI of 42 ± 7.2 at 3 months, 40 ± 6.8 at 6 months, 38 ± 6.4 at 9 months and 35 ± 5 at 12 months of follow ‑up period (p = 0.043).

Conclusion: The combination of metformin + GLP-1 + SGLT2 has many benefits in the metabolic profile of obese patients with DM2 and could be considered as a choice treatment.

Table. Serious adverse events in 403 Endobarrier treated patients.

<table>
<thead>
<tr>
<th>Serious Adverse Event</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early removal because of GI bleed</td>
<td>15</td>
<td>3.7</td>
</tr>
<tr>
<td>Early removal because of liver abscess</td>
<td>4</td>
<td>1.0</td>
</tr>
<tr>
<td>Early removal because of pancreatitis</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>Early removal because of cholecystitis</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>Liver abscess post ‑prolonged ‑implant*</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>5.7</td>
</tr>
</tbody>
</table>

Less severe adverse event

| Precautionary hospitalisation because of transient GI symptoms - removal not required | 12 | 3.0 |
| Early removal because of GI symptoms ‑ Endobarrier had migrated                      | 8  | 2.0 |
| Early removal because of GI symptoms                                               | 8  | 2.0 |
| Minor GI bleeding. Endobarrier not removed                                         | 3  | 0.7 |
| Hospitalisation because of difficult removal - needed two attempts                 | 2  | 0.5 |

Supported By: Association of British Clinical Diabetologists

Supported By: National Institutes of Health (U19TR025744). Boso Family Foundation, Inc.

Racial Differences in Insulin Resistance, Secretion, and Clearance

SUN H. KIM, Stanford, CA

Hispanics and Asians have a higher risk for type 2 diabetes than non-Black whites (NHW); however, the mechanisms remain unclear. We evaluated differences in insulin physiology and the relationship between obesity and insulin action between NHWs (n=68) compared with Hispanics (n=33) and Asians (n=36). All participants were part of our ongoing registry. All were non-diabetic and had the following measurements: 1.) insulin resistance (steady-state plasma glucose, SSPG, using the insulin suppression test, IST); 2.) insulin secretion rate (using the graded-glucose infusion test, GGIIT); and 3.) insulin clearance rate (GGIT). Relationships were compared between measures of obesity (BMI, waist circumference) and SSPG, and between SSPG and insulin secretion rate and clearance rate using multivariate regression. Compared with NHWs, both Hispanics and Asians had higher degrees of insulin resistance than predicted by BMI or WC (Figure, p<0.01). Thus, to achieve the same SSPG concentration, the BMI equivalent of 30 kg/m² in NHWs was 26 in Hispanics and Asians. Insulin secretion and clearance rates were similar for degree of insulin resistance.

In conclusion, higher risk for diabetes in Hispanics and Asians may relate to greater risk for obesity ‑associated insulin resistance.

Supported By: Association of British Clinical Diabetologists

The Positive Effect of the Combination of GLP-1 Analogues and SGLT2 Inhibitors on Obese Patients with Noninsulin ‑Treated DM2

Ioannis L. Matsoukis, Asimina Ganotopoulou, Chrysoyla Triantafillopolou, Konstantina Kanellopoulou, Theodora Athanasopoulou, Alexandra Sianni, Athens, Greece; Piraeus, Greece

Introduction: GLP-1 analogues and SGLT2 inhibitors have complementary mechanisms of action. The aim of the study is to evaluate the results and tolerance of the combination of these medicines.

Purpose: To investigate the effect of the combination of GLP-1 analogues and SGLT2 inhibitors on obese patients with non-insulin ‑treated DM2.

Method: The study included 150 patients, out of which 110 (73.3%) were women with a mean age of 58 ± 5 years and 40 (26.6%) were men with a mean age of 62 ± 6 years, The mean BMI was 36 ± 4 and all patients received oral medication for the treatment of DM2 (metformin ± DPP-4 ± sulfonylureas ± glitazone). The study duration was one year and HbA1c, fasting glucose, body weight, and body mass index (BMI) were measured at 3, 6, 9 and 12 months. Patients changed their medication to metformin + GLP-1 + SGLT2.

Results: A decrease in HbA1c levels were observed at 3 months (mean HbA1c 12 ± 1), at 8 months (mean HbA1c 9 ± 1), at 9 months (mean HbA1c 8.7 ± 1) and at 12 months (mean HbA1c 7 ± 0.8) (p = 0.030). Fasting glucose also showed a gradual reduction in the follow-up tests, namely 185 ± 29mg/dl, 168 ± 22mg/dl, 156 ± 20mg/dl and 145 ± 18mg/dl at 3, 6, 9 and 12 months respectively (p = 0.0045). Similar results were also observed when body weight was measured at 3.6.9 and 12 months (125 ± 18 kg, 108 ± 14 kg, 100 ± 8 kg and 98 ± 8 kg respectively) (p = 0.042). Changes in BMI were also observed with a mean BMI of 42 ± 7.2 at 3 months, 40 ± 6.8 at 6 months, 38 ± 6.4 at 9 months and 35 ± 5 at 12 months of follow-up period (p = 0.043).

Conclusion: The combination of metformin + GLP-1 + SGLT2 has many benefits in the metabolic profile of obese patients with DM2 and could be considered as a choice treatment.

Supported By: Association of British Clinical Diabetologists

Integrated Physiology/Obesity—POSTERS

2097-P

First Risk ‑Benefit Data from the Worldwide Endobarrier Registry

2098-P

The Positive Effect of the Combination of GLP-1 Analogues and SGLT2 Inhibitors on Obese Patients with Noninsulin ‑Treated DM2
Patients’ mean age was 50.8 years and mean baseline A1c was 8.2%. Over two academic medical centers between 2000-2015, using a software tool to identify MS counseling in EMR notes. Counseling and outcomes were an important step in the treatment of DM and obesity.

Methods: We measured fasting serum DKK1 in a pilot study of 159 elderly Afro-Caribbean men (mean age 63.4 years, mean BMI 27.8 kg/m²), a random subset of a population-based study comprising ~3000 African Ancestry men with fasting morning blood collections for biomarker analyses. DKK1 was measured in duplicate in previously unthawed serum with ELISA. Also assessed were anthropometrics, DXA measured adiposity, and lower leg CT measured myosteatosis (intermuscular adiposity (mm²)) and skeletal muscle density (which reflects the intra-muscular fat content (mg/cm²) such that greater intra-muscular adiposity reflects lower muscle density).

Results: In Spearman correlation analysis DKK1 was positively associated with BMI (R=0.19, p=0.01), waist circumference (R=0.15, p=0.05), DXA total body fat (R=-0.22, p=0.004), and DXA trunk fat (R=0.19, p=0.01), independent of age. In addition, DKK1 was associated positively with intermuscular fat (R=0.19, p=0.01), and inversely with muscle density (R=-0.29, p=0.001), independent of age and BMI. No significant association was found between DKK1 and fasting serum glucose and insulin levels, and HOMA-IR.

Conclusion: Our findings suggest for the first time that lower serum levels of DKK1 may be associated with greater overall adiposity, and ectopic skeletal muscle adiposity. Further studies are needed to unravel the potential role of DKK1 in the regulation of body fat among African ancestry and other population groups with a high risk of developing obesity and related metabolic disorders.

Supported By: National Institutes of Health

Metabolic Surgery Counseling, Diabetes Remission, and A1c Control in Patients with Diabetes and Obesity

LEE-SHING CHAN, SHERVIN MALMASI, NAOHJI HOSOMURA, HUABING ZHANG, CHRISTOPHER J. BROWN, VICTOR J. LEI, ALEXA RUBIN, CLARA TING, KIMHYOUB TONG, ALEXANDER TURCHIN, Boston, MA, Beijing, China

Metabolic surgery (MS) can lower A1c and achieve DM remission. Counseling by a healthcare provider is an important initial step in considering MS. We hypothesized that MS counseling results in a significant increase in DM remission and A1c improvement. We retrospectively studied 3,676 adults aged 18-85 with T2DM, BMI ≥ 35 kg/m2, and A1c ≥ 6.5% followed at 2107-P, see page 18.

Methods: We have developed the dual Amplification Refractory Mutation System PCR which amplifies only if 4 CpG sites were all unmethylated. The first ARMS PCR amplifies if 2 CpG sites (+331, 404bp of transcription start sites of INS) are unmethylated simultaneously. This method was applied to 52 patients with type 1 diabetes (T1D) (duration 12.6 ± 10.1 years). We confirmed the positive samples using DNA sequence analysis.

Results: Pancreatic β-cell DNA in the circulation using the Dual Amplification Refractory Mutation System PCR, which amplifies only if 4 CpG sites were unmethylated, was circulating in the long standing T1D, however, the same CpG methylation pattern with these CpG sites are also existing in non-β-cells, thus the false positive results might be involved in these reports.

Conclusion: We have developed the dual ARMS PCR which is a precise method to detect pancreatic β-cell DNA in the circulation.

Supported By: Japan Society for the Promotion of Science

Detection of Pancreatic Beta-Cell DNA in the Circulation Using the Dual Amplification Refractory Mutation System PCR

AKIO KURODA, MISUZU Y. YAMADA, YUKARI TOMINAGA, REKO SUZUKI, MOTOTYUKI TAMAKI, YUKO AKEHI, YUICHI TAKASHI, DAISUKE KOGA, EISUKE SHIMOKITA, FUMINORI TANIHARA, KYOKE KURAHASHI, SUMIKO YOSHIDA, ITSURO ENDO, KEN-ICHI AIHARA, MASAHIRO ABE, KEVIN FERRERI, MUNEHIDE MATSUHISA, Tokushima, Japan, Duarte, CA

Background: Cpg cytosines in the human insulin gene (INS) is uniquely unmethylated in pancreatic β-cells. It has been reported that a few unmethylated Cpg specific PCR in circulating cell-free DNA could detect injury of pancreatic β-cells. However, the same Cpg methylation pattern with these CpG sites are also existing in non-β-cells, thus the false positive results might be involved in these reports. Aim: To develop a precise method for detecting pancreatic β-cell DNA in the circulation.

Methods: We have developed the dual Amplification Refractory Mutation System (ARMS) PCR, which amplifies only if 4 CpG sites were all unmethylated. The first ARMS PCR amplifies if 2 CpG sites (+331, 404bp of transcription start sites of INS) are unmethylated simultaneously, and followed by the second ARMS PCR, which amplifies if 2 CpG sites (+367, 374bp of TSS of INS) are unmethylated simultaneously. This method was applied to 52 patients with type 1 diabetes (T1D) (duration 12.6 ± 10.1 years). We confirmed the positive samples using DNA sequence analysis.

Results: Pancreatic β-cell DNA were detected in 3 T1D (11.8, 2.5, 9.127 copies in 0.1mL of serum) who are diagnosed as slowly progressive T1D, and 16 among healthy control subjects (1.2, 2.2, 1.9, 3.7 copies in 0.1mL of serum).

Conclusion: We have developed the dual ARMS PCR which is a precise method to detect circulating pancreatic β-cell DNA. Almost no β-cell DNA was circulating in the long standing T1D, however, β-cell DNA was detectable in slowly progressive T1D. Also, there were not so many, but a few β-cell DNA in the circulation of healthy control subjects. Therefore, this method is useful to evaluate pathogenesis of type 1 diabetes.

Supported By: National Institutes of Health (4T32HL007609-30)

IER3IP1 Regulates Beta-Cell Survival

JUAN SUN, KENNETH POLONSKY, DECHENG REN, Chicago, IL

Mutations in the gene for Immediate Early Response 3 Interacting Protein 1 (IER3IP1) cause permanent neonatal diabetes mellitus in human. The mechanisms involved have not been determined and the role of IER3IP1 in β-cell survival has not been characterized. In order to determine if there is a molecular link between IER3IP1 deficiency and β-cell survival, we knocked down IER3IP1 gene expression in mouse MIN6 insulinoma cells. IER3IP1 might be involved in these reports.

Supported By: National Institutes of Health (4T32HL007609-30)
Background: Emerging evidence indicates that ectopic skeletal muscle adiposity (i.e., myosteatosis) is greater in African than in European ancestry individuals, and may be a novel risk factor contributing to increased diabetes risk. However, the biological mechanisms underlying myosteatosis are largely unknown. In vitro studies suggest that a Wnt pathway inhibitor, Dickkopf-related protein 1 (DKK1), could be a novel biomarker with a role in adiposity regulation.

Methods: We measured fasting serum DKK1 in a pilot study of 159 elderly Afro-Caribbean men (mean age 63.4 years, mean BMI 27.8 kg/m²), a random subset of a population-based study comprising ~3000 African Ancestry men with fasting morning blood collections for biomarker analyses. DKK1 was measured in duplicate in previously unthawed serum with ELISA. Also assessed were anthropometrics, DXA measured adiposity, and lower leg CT measured myosteatosis (intermuscular adiposity (mm²)) and skeletal muscle density (which reflects the intra-muscular fat content (mg/cm³) such that greater intra-muscular adiposity reflects lower muscle density).

Results: In Spearman correlation analysis DKK1 was positively associated with BMI (R=0.19, p=0.01), waist circumference (R=0.15, p=0.05), DXA total body fat (R=0.22, p=0.004), and DXA trunk fat (R=0.19, p=0.01), independent of age. In addition, DKK1 was associated positively with intermuscular fat (R=0.19, p=0.01), and inversely with muscle density (R=0.29, p<0.001), independent of age and BMI. No significant association was found between DKK1 and fasting serum glucose and insulin levels, and HOMA-IR.

Conclusion: Our findings suggest the first time that lower serum levels of DKK1 may be associated with greater overall adiposity, and ectopic skeletal muscle adiposity. Further studies are needed to unravel the potential role of DKK1 in the regulation of body fat among African ancestry and other population groups with a high risk of developing obesity and related metabolic disorders.

Supported By: National Institutes of Health

Metabolic Surgery Counseling, Diabetes Remission, and A1c Control in Patients with Diabetes and Obesity

LEE-SHING CHAN1, SHERVIN MALMAZI, NAOZHI HOSOMURA, HUABING ZHANG, CHRISTOPHER J. BROWN, VICTOR J. LEI, ALEXA RUBIN, CLARA TING, KIMHYO TONG, ALEXANDER TURCHIN, BOSTON, MA, BEIJING, CHINA

Metabolic surgery (MS) can lower A1c and achieve DM remission. Counseling by a healthcare provider is an important initial step in considering MS. We hypothesized that MS counseling results in a significant increase in DM remission and A1c improvement. We retrospectively studied 3,676 adults aged 18-65 with T2DM, BMI ≥35 kg/m², and A1c ≥6.5% followed at two academic medical centers between 2000-2015, using a software tool to identify MS counseling in EMR notes. Counseling and outcomes were assessed over one and three years after study entry, respectively. Study patients’ mean age was 50.8 years and mean baseline A1c was 8.2%. Over one year after study entry, 20.2% of patients had MS counseling. In univariate analyses, patients who received MS counseling had a higher rate of DM remission (A1c<6.5% and no DM medications besides metformin) and were more likely to have achieved A1c control (<7.0%) vs. those who did not (Figure. In multivariable analyses adjusted for patient demographics and comorbidities, MS counseling was associated with an OR of 1.43 (95% CI 1.11-1.84; p=0.005) for achieving DM remission and an OR of 1.44 (95% CI 1.15-1.81; p=0.005) for achieving A1c control. In this large study of patients with T2DM and obesity, MS counseling was associated with significantly greater rates of DM remission and A1c control. These findings suggest MS counseling is an important step in the treatment of DM and obesity.

Supported By: National Institutes of Health (4T32DK007609-30)
suppression induced apoptotic cell death which was associated with an increase in expression of the BH3-only molecule Bim. Knockdown of Bim reduced apoptotic β-cell death induced by IER3IP1 suppression. Overexpression of the anti-apoptotic molecule Bcl-xL prevents β-cell death induced by IER3IP1 suppression. Moreover, IER3IP1 also regulates activation of the unfolded protein response (UPR). IER3IP1 suppression impairs the IRE1α and PERK arms of UPR. These results suggest that IER3IP1 suppression induces β-cell death by upregulating Bim and decreasing UPR activation. The studies in vivo also show the beta cell specific knockout IER3IP1 mice develop diabetes related to beta cell death and insulin secretion defect.

Supported By: University of Chicago (P50DK020598)

2104-P

Targeted Deletion of ATF4 in β Cells Leads to the Vulnerability and Dedifferentiation during ER Stress

KESUKE KITAOKA, KYOKE KURASHI, MASATO MIYAKE, YOSHIMASA HAMADA, MIHO OYADOMARI, SEIDICHI OYADOMARI, Tokushima, Japan

ATF4 is the main transcriptional regulator of the Unfolded Protein Response (UPR) that promote restoration of normal ER function, although the contribution of ATF4 on β-cells remains poorly understood. Therefore, we developed mature β-cell specific ATF4 knockout mice (βATF4KO), which were crossed with mice expressing Cre recombinase under the control of insulin promoter. ATF4-deleted β-cells were comparable to WT under normal condition but were susceptible to ER stress. To examine the role of ATF4 in vivo, we bred the Akita insulin folding mutation onto βATF4KO background. Akita/βATF4KO were dramatically compromised by overt hyperglycemia in their early age and remarkable short life span due to ketoacidosis. Interestingly, we found that increased number of cells staining for glucagon, somatostatin or pancreatic polypeptide in the islets of Akita/βATF4KO, suggesting the increased β-cell dedifferentiation. We further employed the gain-of-function study using β-cell specific transgenic mice expressing Fv2E-PERK, which can activate PERK/ATF4 signaling upon addition of the artificial ligand. The induced activation of PERK/ATF4 signaling resulted in reduced insulin secretion without any sign of β-cell apoptosis. Microarray analysis revealed that several key β-cell specific transcription genes such as Pdx1 and Mafa were inhibited by the activation of PERK/ATF4 signaling. We demonstrated that ATF4-deleted β-cells are more vulnerable to dedifferentiation during ER stress and excess ATF4 has inhibitory effect in β-cell function. Overall, our study has uncovered that the importance of ATF4 in governing β-cell adaptation and resilience during ER stress.

2105-P

Metabolic Insufficiency Caused By Cellular Stresses Is Implicated in Beta-Cell Dedifferentiation in the Mouse Model of Wolfram Syndrome

KIKUKO AMO-SHIINOKI, KATSUYA TANABE, MASAYUKI HATANAKA, YUKIO TANIZAWA, Ube, Japan

Pancreatic β-cell loss is associated with augmented ER and oxidative stresses in Wolfram syndrome caused by mutations in the WFS1. In the Wfs1-/- mice, β-cells become dedifferentiated and revert to endocrine progenitor cells, and a subset of them takes alpha cell fate. Such β-cell plasticity appears after nursing, independently of hyperglycemia, and becomes more apparent along with diabetes progression accompanied with no significant increase in apoptosis. We have found that genetic inhibition of Txnip, which is a stress response molecule involving in various cellular processes, preserved β-cell mass and maintained glucose homeostasis in the Wfs1-/- mice. This suggests its roles in the regulation of β-cell plasticity in the setting of Wfs1 deficiency. One clue to the mechanisms underlying beta cell dedifferentiation was the paradoxical reduction of acetyl-CoA, citrate and ATP content in the Wfs1-/- islets in spite of the enhanced glycolysis with an increase in pyruvate. This metabolic dissociation was correlated with an increase in phosphorylated pyruvate dehydrogenase (PDH). Importantly, Txnip directly interacts with both PDH kinase and PDH, indicating its involvement in the regulation of PDH activity. Indeed, islets of Wfs1-/- mice lacking Txnip demonstrated a robust reduction of phosphorylated PDH and a restoration of capabilities of ATP production in response to glucose. Thus, these findings illustrate impaired energy metabolism in β-cells under the chronic stress conditions and suggest that β-cells may possibly become dedifferentiated to adapt to metabolic insufficiency caused by unresolved stresses. This provides new insights into molecular mechanisms underlying beta cell loss in diabetes related to cellular stresses, such as Wolfram syndrome.

Supported By: Japan Society for the Promotion of Science (16K09752 to K.T.), (23H08080, 15H04849 to Y.T.), (15K21188 to K.S.), (15K09390 to M.H.) Takeda

Science Foundation (to Y.T.), Novo Nordisk Pharma Ltd. (to K.S.), Japan Association for Diabetes Education and Care (to K.S.), Banyu Life Sciences Foundation International (to K.S.)

2106-P

Injury Factors Alter miRNAs Profiles of Exosomes Derived from Islets and Circulation

QI FU, HEMIN JIANG, TAO YANG, Nanjing, China, Jiangsu, China

Islets damage is a major abnormality underlying diabetes, thus timely monitoring islets destruction is critically needed. Recent studies discovered the biological functions of exosomes and suggested the value of exosomes in disease diagnosis and prognosis. This study aimed to investigate the impact of injury factors on the miRNA profiles of islet exosomes and determine whether circulating exosomal miRNAs would be suitable as biomarkers of islet cell damage. Islets were isolated from ICR mice and induced injury in vitro by mixed cytokines (TNFα, IL-1β and IFNγ) and streptozotocin (STZ) and exosomes were derived from the cultural supernatant. Using miRNA microarray analysis, we found 22 and 11 differentially expressed miRNAs in islet exosomes of STZ and cytokines treatment, respectively. B differentially expressed exosomal miRNAs were found both in STZ and cytokines treated group, and miR-375-3p and miR-125-5p were validated by quantitative RT-PCR. Serum exosomes were isolated from ICR mice of islets damage in vivo induced by STZ injection and subjects with various glucose metabolism states and diabetic duration. Quantitative RT-PCR demonstrated exosomal miR-375-3p dramatically increased in serum of STZ treated mouse prior to the turbulence of blood compromises and serum insulin. In human serum exosomes, miR-375-3p was elevated in newly-onset diabetes patients. Overall, our results suggest that injury factors cytokines and STZ affected the miRNA profiles of exosomes derived from islets and exosomal miR-375-3p showed promising potential as a biomarker of islets damage. Further studies were necessary to purify islet-specific exosomes from circulation for improving the accuracy.

Supported By: Natural National Science Foundation of China (81530026, 81600840)

2107-P

Tissue Plasminogen Activator (tPA) Expression Is Increased by Islet Amyloid Formation In Vitro

NATHALIE ESSER, MEGHAN F. HOGAN, ANDREW T. TEMPLIN, MARK ZIEMANN, ASSAM EL-OSTA, SAKENEH ZRAIKA, REBECCA C. HULL, STEVEN E. KAHN, Seattle, WA, Melbourne, Australia

Islet amyloid deposition is a pathologic hallmark of type 2 diabetes (T2D) resulting in β-cell loss. tPA, an activator of fibrinolysis, attenuates brain amyloid deposition associated with Alzheimer’s disease. Based on RNAseq analysis to identify genes upregulated by islet amyloid, we found tPA to be specifically increased in islets with amyloid deposition (FDR=6.23 E-40). We therefore determined whether tPA expression is explicitly regulated by islet amyloid formation and thus could impact islet pathology in T2D. Using a transgenic mouse expressing human islet amyloid polyepitide (hAPP) in β cells, a model of islet amyloid formation, and mice expressing non-amyloidogenic mouse IAPP (mpIAPP) as control, we measured tPA mRNA expression in islets during amyloid formation. Isolated islets were cultured for up to 7 days in 11.1 or 16.7 mM glucose, the latter to induce amyloid deposition in hAPP islets. Under amyloidogenic conditions, tPA gene expression increased 2-fold after 2 days of culture and was further elevated at 7 days in hAPP compared to mpIAPP islets (7.5±1.4 vs. 1.2±0.1, n=4, p<0.001). This increase at 7 days was not observed in hAPP islets cultured under non-amyloidogenic conditions (1.1±0.5 vs. 7.6±1.4 in 11.1 vs. 16.7 mM glucose, respectively, n=4, p<0.001). When cultured in 16.7 mM glucose with an amyloid inhibitor (200 µM Congo Red [CRI]), tPA gene expression was abrogated in hAPP transgenic islets (1.5±0.3 vs. without CR, respectively, n=4, p<0.001), implying tPA gene expression is regulated downstream of amyloid formation. Immunoblot confirmed the presence of tPA protein in islets but not in a β-cell line, and islet immunohistochemistry showed it did not co-localize with insulin, suggesting it is likely that tPA is not produced in β-cells. In summary, we identified the fibrinolytic activator tPA to be upregulated with amyloid formation in islets. Thus, modulating tPA expression could reduce the deleterious impact of islet amyloid on β-cell mass in T2D.

Supported By: Belgian-American Educational Foundation; Baillet Latour Foundation; Belgian Association of Diabetes; French Society of Diabetes; Leon Fredericq Foundation; Horst-Dapsens Foundation

A552

Moderated Poster Discussion  ADA-Supported Research
2018-P

The Effect of nAChR Signaling on Terminal-Undfolded Protein Response under Endoplasmic Reticulum Stress in INS1 Cells

TASUYA ISIBASHI, SHUHEI MORITA, ASAKO DOI, HIROSHI IWAKURA, HIROYUKI ARIYASU, MASAHIRO NISHI, HIROTU FURUTA, TAKASHI AKAMIZU, Wakiyama Institution

Background: Pancreatic β-cells are specialized for the production of insulin and susceptible to endoplasmic reticulum (ER) stress. Irreversible ER stress is coupled with terminal-undfolded protein response (T-UPR) through activating Ire1α, which leads to β-cell dysfunction and apoptosis. Previous reports show the effects of nAChR signaling against ER stress-induced neurotoxicity. However, it is still unknown if and how nAChR signaling affects T-UPR in β-cells. The aim of the study is to determine if and how nAChR signaling reduces T-UPR by regulating Ire1α expression in β-cells.

Methods: We investigate the role of nAChR signaling on T-UPR signaling under ER stress or specific Ire1α activation using rat insulinoma cell line, INS-1. Cells were treated with Nicotine, an agonist of nAChR, α-Bungarotoxin (α-BTX); an antagonist of nAChR αβ subunit, and Tunicamycin (Tm) and Thapsigargin (Tg) ER stress inducers. Expression levels of spliced XBP1 and TNXIP/Insulin (Proinsulin), as T-UPR markers, were analyzed by real-time PCR and/or Western blotting.

Results: We first confirmed the expression levels of nAChR αβ subunits in INS1 cells. ER stress inducers (Tm or Tg) increased XBP1-splicing, and Nicotine (≥10 μM) reduced it. Nicotine reversed ER-stress-induced increase of TNXIP and decrease of Insulin1 (proinsulin) expression in both mRNA and protein levels. Further, Nicotine reversed increased expression of TNXIP and decrease of Insulin1 mRNA expression level induced by Ire1α overexpression in Dox-inducible wild type Ire1α-overexpressing INS1 cells. Those effects of Nicotine were canceled by α-BTX.

Conclusion: Our results suggest that nAChR signaling could prevent T-UPR induced by ER stress in INS1 cells.

2019-P

GDF15 Is Induced by T1D-Associated Cytokines and ER Stress and Promotes Beta-Cell Apoptosis

GUANLIAN XU, LANCE THIELEN, JUNJIN CHEN, SEONGHO JO, ANATH Shtely, Birmingham, AL

Type 1 diabetes (T1D) is characterized by T-cell and cytokine-mediated pancreatic beta cell loss, but some of the mechanisms involved are still unknown. Growth differentiation factor 15 (GDF15), which is a distant member of the transforming growth factor β (TGFβ) family, has been shown to be increased in various diseases including cancer, heart failure and type 2 diabetes and to promote cancer cell apoptosis. Although we found that GDF15 is highly expressed in adult human beta cells, its role in beta cells and T1D has not been studied. In the present study, we found that GDF15 is significantly elevated in the islets of diabetic female NOD mice compared to non-diabetic female NOR and male NOD mice. In addition, by using human islets, Akita beta cells and INS-1 beta cells, we found that the expression and content of GDF15 are significantly increased by T1D-associated cytokines and thapsigargin/ER stress. Furthermore, we demonstrated that GDF15 knockdown significantly blunts cytokine-induced beta cell apoptosis, while GDF15 overexpression exacerbates T1D-associated cytokines-induced beta cell apoptosis. Taken together, these findings suggest that GDF15 is induced by cytokine-induced ER-stress in beta cells and might contribute to the beta cell loss in T1D. Targeting beta cell GDF15 may therefore represent a novel strategy to inhibit beta cell loss in T1D.

Supported By: National Institutes of Health, JDRF

2108-P

MODY Signal Pathway in the Endoplasmic Reticulum Stress and the Role of nAChR in the Glucolipotoxicity of INS-1 3 Cells

VANAN DONG, YUKUN LI, JIANZHONG XIAO, Beijing, China; Shijiazhuang, China

Metabolic disturbances induce endoplasmic reticulum stress (ERS) in pancreatic beta cells. This study aims to investigate whether a common pathway exists in the ERS induced by various chemicals, including high levels of glucose and palmitate. ERS in INS-1 3 cells was induced by exposure cells to thapsigargin (TG), tunicamycin (TM) or palmitic acid (PA) high glucose (HG). Digital gene expression (DGE) profiling technique was used to detect differentially expressed genes. The profile of gene expression was detected by gene ontology (GO) function and pathway enrichment analysis. On the basis of DGE results, Nkx6.1 over-expression was confirmed in INS-1 3 cells lines by lentivirus infection to explore the importance of the findings. Real time reverse transcription polymerase chain reaction (RT-PCR) was used to verify the expression changes of key genes. Cell viability was measured by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. And the apoptosis was detected by flow cytometry. Glucose stimulates insulin secretion (GSIS) was used to measure the INS-1 3 cell function. DGE demonstrated that there were 135, 57 and 74 differentially expressed genes in TG, TM and HG+PA groups, respectively. Genes that were differentially expressed were enriched to endoplasmic reticulum stress, antigen processing and presentation, and protein export pathways, and surprisingly, the majority onset diabetes of the young (MODY) pathway. Nkx6.1 is a common abnormal-expressed gene in MODY signaling pathway among TM, TG and HG+PA groups. Apoptosis was ameliorated by 45.4% and proliferation was increased by 40.3% in the Nkx6.1 over-expression cells exposed to high level of glucose and palmitate. At the same time, both basal and glucose stimulated insulin secretion increased by 2.09 and 1.82 folds, respectively. ERS changed the expression of MOD1 pathway genes. Over-expression of Nkx6.1 protected the INS-1 3 cells from glucolipotoxicity.

Supported By: National Natural Science Foundation of China (81370911)

National Basic Research Program of China (2011CB604003) Tsinghua University (20161080080)

2111-P

Protective Effects of SGLT2 Inhibitor Luseofigliflozin on Pancreatic Beta Cells in Obese Diabetic db/db Mice—“The Earlier and Longer, the Better”

TOMOHIKO KIMURA, MASASHI SHIMODA, SHUHEI NAKANISHI, TOMODATSU MUNE, KOHEI KAKU, HIDEAKI KANETO, Kurashiki, Japan

We recently reported that SGLT2 inhibitor luseofigliflozin (Luseo) preserved beta-cell mass and function in obese diabetic db/db mice. The aim of this study is to compare the protective effects of Luseo on beta-cells between in an early and advanced stage of diabetes. We used 7-week-old and 18-week-old male db/db mice as an early and advanced stage model, respectively. Both mice received Luseo (0.01%) in chow or normal chow for 2 weeks. In addition, we set a long-term administration model (a long-term model) which received Luseo from 7 to 18 weeks old. Blood glucose levels were significantly decreased by Luseo treatment both in the early and advanced stage model. Various β-cell-related gene expression levels, insulin content in islets and glucose-stimulated insulin secretion (GSIS) were enhanced after Luseo treatment in the early stage models which was not clearly observed in the advanced stage model. Immunohistochemical staining showed that beta-cell ratio and percentage of Ki67-positive beta-cells were significantly increased in the early stage model by Luseo treatment which was not clearly observed in the advanced stage model. Furthermore, in the long-term model, blood glucose levels, beta-cell related gene expression levels, insulin content, GSIS, beta-cell ratio and percentage of Ki67-positive beta-cells were markedly enhanced by Luseo treatment. Various parameters were almost completely preserved in the long-term model even when the mice became 18 weeks old. Taken together, protective effects of Luseo on pancreatic beta-cells were more effective in an early stage of diabetes compared to an advanced stage. Surprisingly, administration of Luseo for a prolonged period from an early stage preserved beta-cell mass and function almost completely. These results suggest that long-term administration of Luseo from an early stage is important to maintain the beta-cell mass and function.

2012-P

Targeting Cellular Calcium Homeostasis to Prevent Beta-Cell Death in Type 1 Diabetes

AMY L. CLARK, DAMIEN ABREU, CRIS M. BROWN, FUMIHIKO URANO, St. Louis, MO

Cytokines are important mediators of beta cell death leading to type 1 diabetes (T1DM). The mechanism of cytokine-mediated beta cell death has been previously shown to involve alterations in beta cell calcium homeostasis and increases in endoplasmic reticulum (ER) stress. Our group has previously established that pharmacologic modulation of cellular calcium levels with dantronel and sitagliptin can significantly decrease cytokine and ER stress-mediated activation of the calpain and thioredoxin interacting protein pro-apoptotic pathways and suppress cell death in vitro using INS-1E rat insulinoma cells.

The current study was designed to determine if dantronel and sitagliptin can prevent beta cell death and diabetes in the low dose streptozotocin (STZ) model of T1DM. Male C57Bl/6 mice were treated with 5 doses of STZ (50 mg/kg) daily by 10 days of intraperitoneal (IP) injections of placebo, dantronel, or sitagliptin. Blood sugar was monitored via tail vein blood using a glucometer. Blood glucose and insulin levels in response to 2g/kg IP dextrose injection were obtained on day 10. Unmethylated insulin DNA was also analyzed by real time PCR and/or Western blotting.
Besides, AAT inhibited cytokine-induced JNK activation, caspase 9 cleavage and clathrin-mediated endocytosis, profoundly decreased AAT internalization in a time- and dose-dependent manner. AAT internalization was mediated by β1-antitrypsin (AAT) Protects β Cells via Clathrin-Mediated Endocytosis

JINSUJIN WANG, DO-SUNG KIM, CHARLIE STRANGE, HONGJUN WANG, Charleston, SC

AAT, an acute phase reactant serine protease inhibitor, exerts protective effects on β cells under stress. We reported that AAT inhibits β cell death through the suppression of cytokine-induced c-Jun N-terminal kinases (JNK) activation, in addition to its anti-inflammatory effects extracellularly in an islet transplantation model. To further understand the direct effects of AAT on β cells, we studied AAT endocytosis in human islets and a murine insulinoma cell line, βTC3 cells. We found that AAT was internalized by β cells in a time- and dose-dependent manner. AAT internalization was mediated by clathrin as treatment with chlorpromazine (CPZ), a drug that disrupts clathrin-mediated endocytosis, profoundly decreased AAT internalization. Besides, AAT inhibited cytokine-induced JNK activation, caspase 9 cleavage and DNA fragmentation, which were also overturned by the addition of CPZ. Meanwhile, although evidence suggests that clathrin interacts with autophagy related 16 like 1 (Atg16L1) which results in autophagy in several types of cells, we observed only mild induction of Atg16L1 and autophagy after AAT treatment in β cells.

In summary, as shown in the image, we found that AAT is internalized by β cells via clathrin-mediated endocytosis. Moreover, our finding that AAT endocytosis is required for its protective effects on β cells provides new insight into the usage of AAT-based therapy in diabetes and related diseases.

2111-P

Role of Numb-Mig6 Interactions in Beta-Cell Death during Glucolipotoxicity

HALESHA D. BASAVARAJAPPA, JOSE M. IRIMIA-DOMINGUEZ, PATRICK T. FUEGER, Durham, CA

As the development of type 2 diabetes (T2D) requires a loss of functional beta cell mass, preserving functional beta cell mass is essential for preventing T2D. We have focused our efforts on EGFR receptor (EGFR) signaling because it controls cellular proliferation, survival, and repair/maintenance mechanisms—all features relevant to maintaining beta cell mass—and is dampened during glucolipotoxic conditions (GLT) similar to those in T2D. We have established that Mig6, an endogenous feedback inhibitor of EGFR, is induced in both rodent islets cultured in GLT and human T2D islets. In addition, GLT impairs EGFR signaling in rodent and human islets. Further, Mig6 overexpression promotes apoptosis in both rodent and human beta cell lines and islets. Because Mig6 is an adapter protein and likely functions as a molecular scaffold, here we aimed to define the molecular mechanisms of Mig6 in GLT by identifying the interacting partners of Mig6. We performed mass spectrometry analysis using low-level, flag-tagged Mig6 expression with immunoprecipitation to define the molecular mechanisms of Mig6 in GLT by identifying the interacting partners of Mig6. We performed mass spectrometry analysis using low-level, flag-tagged Mig6 expression with immunoprecipitation to define the molecular mechanisms of Mig6 in GLT by identifying the interacting partners of Mig6. We performed mass spectrometry analysis using low-level, flag-tagged Mig6 expression with immunoprecipitation to define the molecular mechanisms of Mig6 in GLT by identifying the interacting partners of Mig6.

2116-P

Altering β-Cell Proliferation In Vivo by Pharmacological Manipulation of the Nrf2 Pathway

LIGIA S. KATZ, ADOLFO GARCIA-ICANA, DONALD SCOTT, New York, NY

Glucose is a natural mitogen that drives adaptive β-cell mass expansion by promoting proliferation. We previously demonstrated that induction of Nrf2 is required for glucose-stimulated and carbohydrate response element binding protein (ChREBPα)-augmented β-cell proliferation. Here we found that adenoviral delivery of Nrf2 increased human β-cell proliferation by 8.9-fold.

2114-P

Functional Characterization of Wolfram Syndrome 1 Protein in β-Cell Function and Viability

DAMIEN ABREU, ZENO LAUAGNINO, CRIS M. BROWN, DAVID W. PISTON, FUMIHIKO URANO, St. Louis, MO

Endoplasmic reticulum (ER) homeostasis is crucial for proper β-cell function as evidenced by rare monogenic diabetic disorders, such as Wolfram syndrome, arising from genetic defects in key ER molecules. Wolfram syndrome stems from mutation of the ER transmembrane protein, Wolfram Syndrome 1 (WFS1), resulting in a recessive, progressive neurodegenerative disorder that first manifests as juvenile-onset diabetes mellitus (DM). While many WFS1 variants are associated with DM, the role of WFS1 in β-cell viability and function remains unclear. Our central hypothesis is that WFS1 regulates β-cell viability through downregulation of ER stress-responsive pro-apoptotic factors and β-cell function through modulation of key ER Ca2+-transporters. To test this hypothesis, we generated inducible β-cell models of WFS1 knockdown and overexpression using rat insulinoma cell lines to monitor β-cell function and β-cell death. We employed chemical and physiologic stimuli to model ER stress and monitored its downstream effects by real-time PCR, immunoblot and intracellular calcium mobilization. Our data indicate that β-cells depleted of WFS1 exhibit impaired insulin secretion and reduced insulin content. Additionally, knockdown of WFS1 is associated with decreased ER Ca2+, increased cytosolic Ca2+ and increased β-cell death. Conversely, increasing WFS1 expression in vitro increases insulin production and confers protection against ER stress-mediated β-cell death. Our data suggest that WFS1 may preserve β-cell viability by reducing the expression of pro-apoptotic factors CHOP and TRB3. Future studies seek to clarify the mechanisms by which WFS1 protects β-cells against metabolic stressors and promotes insulin production. These studies will expand our understanding of the broader mechanisms by which ER dysfunction triggers β-cell pathology in more common forms of diabetes, and provide potential novel targets for intervention that center on preserving ER homeostasis.

Supported By: National Institutes of Health (HD091107-01A1)

2115-P

Moderated Poster Discussion: Beta-Cell Development and Postnatal Growth (Posters: 2116-P to 2121-P) see page 23.
Deletion of SLC4A4 in Pancreatic β Cells Protects from High-Fat Diet-Induced Glucose Intolerance and β-Cell Dysfunction

MATTHEW BROWN, HEATHER L. HOLMES, KUNTOL RAKSHIT, MICHAEL F. RÖMMER, ALEXSEY MATVEYENKO, Rochester, MN

Islet failure in type 2 diabetes (T2DM) is characterized by loss of glucose-stimulated insulin secretion (GSIS) attributed to β-cell de differentiation (e.g., mis-expression of alpha cell-specific genes). Recent single cell transcriptomics studies identified SLC4A4 (a gene encoding an electroneutral Na+-HCO3¬ cotransporter, NBCe1) as one of the mis-expressed genes in β-cells of patients with T2DM. Thus, we set out to test the hypothesis that mis-expression of SLC4A4 in β-cells contributes to loss of GSIS and impaired glucose homeostasis in T2DM. To address this hypothesis, we first confirmed induction of robust SLC4A4 protein expression in β-cells of patients with T2DM utilizing immunofluorescence staining of autopsy-derived human pancreas specimens. We next generated β-cell-specific slc4a4 knockout (β-slc4a4a−/−) and corresponding control (β-slc4a4a+/+) mice through crossing of slc4a4a−/− and Ins2-Cre mouse models. Adult (3 month old) β-slc4a4a−/− mice displayed normal body weight, glycaemia, glucose tolerance and insulin sensitivity under standard chow fed conditions (p=0.05 vs. β-slc4a4a+/+). In contrast, β-slc4a4a−/− mice exhibited enhanced glucose tolerance and in vivo glucose-stimulated insulin response under conditions of metabolic stress induced by ad libitum intake of 60% high fat diet (HFD) for 8 weeks (p=0.05 vs. β-slc4a4a+/+HFD). Interestingly, improved glucose tolerance in β-slc4a4a−/− mice was also associated with a tendency for expansion of β-cells mass (82%, p=0.09 vs. β-slc4a4a+/+HFD) and increased β-cells proliferation (26%, p=0.11 vs. β-slc4a4a+/+HFD). These results suggest that β-cell mis-expression of the Na+-HCO3¬ co transporter and/or slc4a4a−/− mice contributes to induction of β-cell failure under conditions of metabolic stress and T2DM.
Islet Biology—Beta Cell Development and Postnatal Growth

these genes were greatly blunted when NOTCH inhibition of the PP culture was delayed. Cultures that were kept at the PP state lost endocrine competence when challenged by NOTCH inhibition, and displayed patterning towards exocrine lineages (Duct/ACINAR) as evident through the up-regulation of CF, HNF1B and PROM1. Using the PP population in subsequent DE based computer modeling experiments to optimize for either INS, MIST1 or CF expression demonstrated that NXX1.1 was significantly up-regulated in short term PP cultures optimized for insulin expression as compared to the delayed cultures. Aicar conditions achieved through optimization for MIST1 expression displayed highly increased PFTF1A expression. Finally, PP cultures that were maintained in the absence NOTCH inhibition and subsequently optimized for CF expression displayed increased HNF1B and DBA expression. Altogether this suggests that the lineage specification within the pancreatic field of pluripotent derived cells is partially dictat by the duration a cell spends in a NOTCH active state, confirming findings of the embryonic murine developing organ.

Supported By: American Diabetes Association (1-16-ICTS-053 to J.J.)

2121-P

Ctgf Promotes Differentiation, Regeneration, and Proliferation of β Cells

SHANNON E. TOWNSEND, RAYMOND PASEK, MATTHEW A. COTTAM, MAUREEN A. GANNON, NASHVILLE, TN

One potential model of type 2 diabetes etiology is that those with the disease were born with less β-cell mass making them susceptible to stressors such as obesity. Thus, it would be of therapeutic potential to find mechanisms that increase functional β-cell mass. One candidate that has been studied in our lab is Connective tissue growth factor (Ctgf). Ctgf is a secreted protein known to be involved in cell adhesion, migration and, in some cell types, proliferation. Previous studies in our lab have shown that Ctgf is crucial for β-cell development, with loss of Ctgf resulting in fewer β-cells and decreased β-cell proliferation, thus decreased β-cell mass at birth. Ctgf is also important in situations of metabolic stress, such as pregnancy or β-cell loss. Haploinsufficiency during pregnancy results in decreased maternal β-cell proliferation while in contrast, over-expression of Ctgf results in increased β-cell proliferation and regeneration in a model of partial β-cell ablation. Treatment of human and mouse islets ex vivo with recombinant human Ctgf (rHCTGF) has resulted in increased β-cell proliferation. To determine whether smaller fragments of the 40 kD Ctgf protein can promote proliferation, mouse and human islets were treated with either an N- or C-terminal fragment independently.

Results show that N-terminal Ctgf is responsible for promoting β-cell proliferation in both mouse and human islets. Further studies will elucidate the mechanisms by which Ctgf promotes β-cell proliferation as well as through what receptor it acts on β-cells.

Supported By: American Diabetes Association (7-16-B5S-100 to M.A.O.1 U.S. Department of Veterans Affairs (10IB08003744-01)

2122-P

Mig6 Is Required for Pancreas Development in Zebrafish

KIMBERLEY E. FRIEGER, RYAN M. ANDERSON, Indianapolis, IN, DURANT, CA

Aim: We tried to investigate longitudinal change in BCM of diabetic model mice administered with SGLT2 inhibitor using in-vivo SPECT/CT imaging with 111In-Labeled Exendin-4.

Noninvasive Longitudinal Evaluation of GPR ‑119 Agonist Effects on β‑Cell Mass Using GLP‑1 Receptor-Targeting SPECT/CT

Aims: Type 2 diabetes mellitus (T2DM) is known as a progressive disease with loss of pancreatic β-cell mass (BCM) and functions. However, longitudinal changes of BCM remain veiled since non-invasive techniques for observation of BCM in vivo have not been established. We developed [Lys4][111In-Bn0TPA-Ahx]exendin-4 ([111In]Ex4) targeting the glucagon-like peptide 1 (GLP-1) receptor, which enabled to quantify BCM non-invasively. DS8500a, a G protein-coupled receptor 119 (GPR119) agonist, is under investigation for the treatment of T2DM. Some GPR119 agonists showed the possible stimulation of β-cell replication, which suggested some preferable effects of GPR119 agonists on BCM. Therefore, we investigated this GPR119 agonist effect on BCM in diabetic mice using our [111In]Ex4 SPECT/CT technique.

Method: Five -week-old male db/db mice with dietary restriction were assigned to the following two groups: mice fed with normal chow (group C) and those with DS8500a-dosed chow (group DS). We performed [111In-Ex4 SPECT/CT every four weeks until 13 weeks old and evaluated the RI accumulations in the pancreas. Ex-νivo pancreatic RI intensities, together with pathological and immunohistochemical analysis of BCM were also examined.

Results: As for [111In-Ex4 SPECT/CT, pancreatic RI intensities in group DS were significantly higher than those of group C, at the age of 9 and 13 weeks old. Moreover, ex-νivo pancreatic RI intensities in group DS were significantly higher than those of group C. Pathological BCM analysis revealed significantly larger BCM in group DS than in group C.

Conclusion: [111In-Ex4 SPECT/CT as well as ex-νivo pancreatic analysis showed preserved BCM in mice with DS8500a. This result was corroborated by the conventional pathological method. Taken together, [111In-Ex4 SPECT/CT showed DS8500a, a GPR119 agonist, could attenuate the progression of BCM loss in diabetic mice.

Supported By: Daiichi Sankyo

2124-P

Investigation on the Protective Effect of Canagliflozin on Pancreatic Beta-Cell Mass Using SPECT/CT Imaging with 111In-Labeled Exendin-4

KEITA HAMAMATSU, HIROYUKI FUMIYOTO, NAOKIKA FUJII, TAKAHIRO MURAKAMI, MASASHIRO SHIOHAMA, HIDEKI SAJI, NOBUYA INAGAKI, KYOTO, JAPAN

Aims: Type 2 diabetes mellitus is known as a progressive disease with loss of pancreatic β-cell mass (BCM) and functions. However, longitudinal changes of BCM remain veiled since non-invasive techniques for observation of BCM in vivo have not been established. We developed [Lys4][111In-Bn0TPA-Ahx]exendin-4 ([111In]Ex4) as a radioactive probe targeting to the glucagon-like peptide-1 receptor with the aim of quantifying BCM by the measurement of probe accumulation in the pancreas. In this study, we investigated the protective effect of sodium-glucose co-transporter-2 (SGLT2) inhibitor on BCM using in-vivo SPECT/CT imaging with this probe.

Aim: We tried to investigate longitudinal change in BCM of diabetic model mice administered with SGLT2 inhibitor using in-vivo SPECT/CT imaging with [111In]Ex4.

Method: Male db/db mice were assigned into two groups: canagliflozin-administered group (group A) and non-administration group (group B). In-vivo SPECT/CT scans were performed before and after the intervention. The pancreatic uptake of [111In]Ex4 was evaluated using ROI with > 40% of the volume of the whole pancreas with the exception of the peripheral space.

Result: The pancreatic uptake was significantly decreased in group B, on the other hand, no significant change was observed in group A. After the intervention, the pancreatic uptake was significantly higher in group A than group B.
Discussion: SPECT/CT imaging analysis indicated that BCM was significantly larger in group A than group B after the intervention. It is considered that this difference was made by the protective effect of canagliflozin on BCM.

Conclusion: It is considered that the protective effect of canagliflozin on BCM could be investigated using in-vivo SPECT/CT imaging with [111mIn]ExA. Supported By: Mitsubishi Tanabe Pharma Corporation

Suppression of STAT3 Signaling Promotes Acinar-to-β Reprogramming Induced by Distinct Transcription Factors
MASAKI MIURA, TAKESHI MIYATSUKA, SHUGO SASAKI, TAKEHIRO KATAHIRA, LUKA SUZUKI, MIWA HIMURO, YUYA NISHIDA, YOSHIO FUJITA, KIYOMI Matsuoka, HIROTAKA WATADA, Tokyo, Japan, Vancouver, BC, Canada, Maebashi, Japan, Saita, Japan
Aims: Uncovering pancreas development has helped us to explore efficient methods to generate surrogate cell-based cure for diabetes. Since it has been demonstrated that Stat3 plays a role in the plasticity of pancreatic acinar cells (Miya et al. Genes Dev. 2006), we investigated the possibility that Stat3 signaling affects the cellular reprogramming of pancreatic cells into β-cells in vitro and in vivo.
Methods: The combined expression of the defined transcription factors Ptx1, Neurog3, and Mafa induced the pancreatic progenitor-like mPAC cells in vitro and in the mouse models in vivo, and Stat3 signaling was modulated using Stat3 inhibitor, adenoviruses expressing dominant negative or constitutively active form of Stat3, and Stat3 deletion. Results: Whereas phosphorylation of Stat3 (pStat3) was induced by adenoviral vectors expressing Ptx1 or Mafa, most of the reprogrammed β-cells induced by a polycistronic adenoviral vector carrying Ptx1-Neurog3-Mafa cassette (Ad-FNM) were negative for pStat3. On the other hand, suppression of pStat3, using Stat3 inhibitor BP-1-102 or dominant-negative form of Stat3, significantly enhanced β-cell neogenesis by Ad-FNM, whereas a constitutively active form of Stat3 decreased the reprogramming efficiency into β-cells. In order to confirm the role of Stat3 in vivo, we generated a transgenic mouse line “acinar-FNM,” which ectopically expressed Ptx1, Neurog3, and Mafa in acinar cells, and found that Stat3 deletion significantly increased the number of newly differentiated β-cells in acinar-FNM mice. Furthermore, Stat3 inhibition by BP-1-102 in vivo efficiently induced β-cell neogenesis by Ad-FNM and ameliorated hyperglycemia in alloxan-induced diabetic mice.
Conclusions: Stat3 signaling is suppressed in newly-generated β-cells induced by distinct transcription factors, and Stat3 inhibition promotes the reprogramming efficiency into β-cells, which could lead to future cell therapy for cure of diabetes.

E-Cadherin Downregulation by Cathepsin L Plays a Role in the Proliferation of Insulin-Producing Cells following Inhibition of Serpin B13
CHI-WEN LI, TZONG-JEN SHEU, JAN CZYZYK, Rochester, NY
Experiments targeting of the exocrine pancreatic ductal tree stimulates beta-cell rejuvenation thereby underscoring the importance of functional crosstalk between the exocrine and endocrine pancreas. We recently found that antibody directed against serpin B13, a protease inhibitor expressed in the ductal epithelium of the exocrine pancreas, increased the catalytic activity of its protease target, cathepsin L (CatL) and subsequently upregulated E-cadherin levels during islet formation of Stat3, significantly enhanced β-cell proliferation, and Reg upregulation has been shown to be involved in the pathophysiology of diabetes. Although such findings highlight the need for better understanding of α-cell biology, it remains to be elucidated where α-cells originate and what regulates α-cell fate: α-cell neogenesis, maturation and dedifferentiation. To address this issue, we generated a novel reporter mouse “Gcg-Timer.” Methods: We have previously generated Neurog3-Timer mouse (Miya et al. Diabetes 2009), in which newborn endocrine cells can be sorted by FACS separately from differentiated cells. However, we failed to obtain spatiotemporal information of newborn cells due to the low fluorescent intensity of DiRed-ES. To overcome this difficulty, we used a new reporter construct eGFP-IRES-mRFP and inserted it into the proglucagon gene. In this Gcg-Timer mouse, green fluorescence can be detected first, because mRFP expression is controlled by IRES and is therefore lower than eGFP expression. As a result, newly-generated α-cells exhibit green fluorescence and can be distinguished from more differentiated α-cells exhibiting both green and red fluorescence.
Results: Both microscopic analysis and flow cytometry revealed that green-dominant α-cells were observed in Gcg-Timer mice at embryonic and neonatal stages until postnatal day 3 (P3), but not at P14 and adult stages. Intriguingly, red dominant cells, which were negative for glucagon staining, were detected at P14, indicating that α-to-non-α transition occurs at this stage.
Conclusions: Gcg-Timer mice enabled us to label not only newly-generated α-cells but also dedifferentiated α-cells in a time-dependent manner. The α-cell neogenesis occurs specifically during embryonic and early neonatal stages under physiological conditions. Supported by: Japan Ministry of Education, Culture, Sports, Science and Technology (16H05630)

Unusual Duct-Like Cells in the Islet of Diabetic C414A-CRY1 Transgenic Mice
SATOSHI OKANO, AKIRA YASUI, SHIN-ICHIRO KANO, KENNICHI SATOH, MASAKI IGARASHI, OSAMU NAKAJIMA, Yamagata, Japan, Sendai, Japan
Cryptochrome (CRY) proteins play indispensable roles in the mammalian circadian clock. We previously generated transgenic mice ubiquitously expressing mCRY1 with a mutation in cysteine414 (the zinc-binding site of CRY1). The Tg mice overexpressing the mutant CRY1 (C414A-CRY1) showed early onset diabetes mellitus characterized by β-cell dysfunction in addition to unusual circadian rhythms in locomotor activities. We have already shown that the decrease of insulin secretion from β-cells along with the lowered proliferation of β-cells due to the senescence-associated secretory phenotype (SASP)-like changes in the Tg mice (Okano S., 2018). We have also demonstrated that, atypical duct-like structures having some common morphological characters to pancreatic intraepithelial neoplasias (PanINs) that can cause pancreatic ductal adenocarcinoma, frequently appeared in the aged Tg mice. In this study, to explore the relation between the unique features of β-cells and the generation of PanIN-like structures, we further performed detailed studies of the pancreases of Tg mice. We found that unusual duct-like structures producing mucin emerged not only in the exocrine organ areas but also in the inside of the islet. These results may suggest that islet cells in the Tg mice can transdifferentiate into duct-like cells, thereby contributing to generate PanIN-like lesions in the Tg mice. In addition, the extent of fibrosis in the islet increased in the Tg mice compared with wild type controls. Taken together, our results suggest the SASP-like microenvironment in the islet play some roles to modify the integrity of endocrine cells as well as the architecture of the islet.
Supported By: Japan Society for the Promotion of Science; Tokoh University
Islet Biology—Beta Cell—Development and Postnatal Growth

2129-P

Adverse Impact of Hashimoto’s Thyroiditis on Pancreatic Beta-Cell Function in Type 2 Diabetic Patients

YUANYUAN ZHANG, RONGXIN SUN, LUJIE ZHANG, YUAN FANG, CAI GAO, YU, SHASHA YUAN, YINGMEI FENG, DONG ZHAO, Beijing, China

Background: Hashimoto’s thyroiditis (HT) is an autoimmune disease and often coexists with other metabolic disorders. It has been shown that HT patients have higher levels of antibodies against proinsulin than controls. The incidence of HT in T2DM patients is unclear and has never been studied whether beta cell function differ between T2DM patients alone and complicated with HT.

Methods: 80 T2DM patients who were recruited between November 2015 till June 2016 to Endocrinology Center in Lu He hospital were analyzed. HT was diagnosed if either serum TPO antibody or TG antibody exceeded the normal range. After a 12-hour overnight fast, venous blood samples were obtained to measure total cholesterol, triglyceride, HDL-c, CRP, insulin and Scr. Oral glucose tolerance test (OGTT) was examined in the patients and serum-c-peptide levels were quantified at 0, 1, 2, and 3 hours after glucose administration.

Results: 80 T2DM patients were included in the study. 249 patients were diagnosed HT. Compared with non-HT subjects, T2DM with HT were more males (44.7% vs. 35.2%, p<0.00) and had higher values of systolic blood pressure (133.8 mm Hg vs. 131.1 mmHg, p<0.03). Although age, body mass index, HbA1c, serum cholesterol and triglyceride did not differ between two groups (p>0.17 for all), fasting C-peptide levels were lower in T2DM complicated with HT than T2DM alone (1.09 ±0.90 nmol/L vs. 1.28±0.98 nmol/L, p=0.004). To further compare beta cell function, patients were performed OGTT test. Serum-C peptide levels remained lower at 1 and 2 hours after oral administration of 75-g glucose in T2DM with HT than T2DM alone (1 hour: 2.10±1.77 nmol/L vs. 2.33 ±1.84 nmol/L, p<0.03; 2 hours: 3.04±2.56 vs. 3.47±2.77 nmol/L, p=0.02). Serum-C peptide levels were comparable three hours after 75-g glucose intake (3.16±2.45 nmol/L vs. 3.50±2.78 nmol/L, p=0.49).

Conclusion: The prevalence of HT is relatively high in T2DM patients, which was associated with reduced beta cell function.

2130-P

GLP-1 Controls Pancreatic Endocrine Development

CORENTIN M.H. CRAS-MÉNEUR, RANDY J. SEELEY, Ann Arbor, MI

Glucagon-like peptide 1 (GLP-1) has been successfully leveraged as a tool to gain functional insight into the maturation of islets and the beta cell. Initial studies in this field were performed using organotypic culture models (liver and kidney), or wild-type and beta cell-specific GLP-1R KO mice. These were also limited by their inability to extend analysis directly to the cell population level. We therefore set out to study islet development from a single cell level in both human and rat. Understanding the functional maturation of β-cells during the fetal and neonatal period, coupled with the insight into the molecular mechanisms responsible for this maturation, can lead of the development of molecular markers of a dysregulated β-cell function that may persist beyond early neonatal period.

Supported By: American Diabetes Association (1-16-JFD-086 to D.E.S.)

2132-P

Synergistic Effects of Long-Term Combination Therapy of DPP-4 Inhibitor and SGLT2 Inhibitor on the Preservation of Beta-Cell Volume in Rats with Type 2 Diabetes

HIROKI MIZUKAMI, GANYANG SUO, KAZUHIRO TAKAHASHI, SONG OSONO, SAORI OGASAWARA, WATARIUNA INUI, HOKKAIDO, Japan

One of the main pathogenetic features of type 2 diabetes (T2D) is reduction of β cell volume (Vβ). Several anti-diabetic oral agents were shown to improve Vβ in experimental studies. While DPP-4 inhibitor (DPi) ameliorated Vβ possibly via the action of GLP-1, recent studies reported that SGLT2 inhibitor (SGi) may facilitate GLP-1 secretion from L cells. These findings raised a hypothesis that the combination therapy (CT) of DPi and SGi may potenti- ate the effects of DPi on Vβ. To explore this possibility, we recruited non-obese spontaneous T2D Goto-Kakizaki (GT) rats and control Wistar rats (WR) at 5 weeks of age. GK was divided into DPi treated group (GTPi) (10mg/kg teneiglitsin), SGi-treated group (GCa) (10mg/kg canagliflozin) and CT group (GTeCa). During experimental period, diabetic state was evaluated by gly- cated Hb (gHb), 2g/kg oral glucose tolerance test (OGTT), glucose-stimulated insulin secretion test (GSIS) and serum active GLP-1. At end, pancreata were underwent for the pathological evaluation of each endocrine cell volume by tetra-immerhistochemistry. Over 24 weeks of treatment, GK showed higher gHb and deteriorated OGTT (p<0.01 vs. W). Although DPi and SGi in each sig- nificantly improved gHb and OGTT compared to GK, the effect was the most marked in GTeCa. Of note, active GLP-1 was the highest in GTeCa among all groups (p<0.05 vs. GTe), while the level in GTe was higher than in W, GK, and GCa (p<0.01). GK showed attenuated GSIS (p<0.01 vs. W). It was signifi- cantly improved in GTe and GTeCa compared to GK (p<0.05 vs. GTe, p<0.01 vs. GTeCa), although it was comparable between GK and GTe. Pathological evaluation disclosed a significant decrease in Vβ in G (p<0.01 vs. W). Vβ was the most well-preserved in GTeCa (p<0.05 vs. GTe), followed by GTe (p<0.05 vs. GK), while it was comparable between GK and GTe. Our findings suggest that CT of DPi and SGi is more effective for β cell function and pathology in T2D than the monotherapy of DPi or SGi.

2133-P

Lactational Programming of Offspring Glucose Homeostasis and Body Composition by Early Postnatal Metformin Exposure

BRIGID GREGG, Ann Arbor, MI

Background: The early postnatal period is a critical window for programing of long-term metabolic health. Our previous studies showed that gestational metformin exposure increased pancreatic beta-cell fraction in birth and improves glucose homeostasis in adulthood.

Hypothesis: We hypothesized that metformin administration to dams during the critical window of lactation would alter neonatal nutrient exposure and the acquisition of the gut microbiome from the mother leading to a per- manent change in offspring metabolic tissues.

Methods: We used C57Bl/6J mice for the developmental programming studies in this experiment. Metformin was delivered in drinking water to pregnant dams from postnatal day 1 (P1) and continued through the lactation period to P21 (Met PN group). Offspring were examined during lactation and as adults. Dams were examined during lactation and upon weaning. Gut microbiome com- position was determined by 16s sequencing in dams and offspring.

Results: Dams on metformin showed improved glucose tolerance at weaning. Met PN pups had lower body weights that began during the first...
3 weeks of life and persisted to 6 months. On intraperitoneal glucose tolerance testing male but not female offspring had improved glucose responses at 2 months and increased glucose stimulated insulin secretion. Met PN offspring had a lower body fat percentage at necropsy. Stool microbiome studies showed that Met PN pups had an altered intestinal colonization that persisted into adulthood with an increase in the bacteroides:firmicutes ratio at the time the lower weight trajectory was established. A lower bacteroides:firmicutes ratio has been associated with obesity.

Conclusions: These findings suggest that limited early postnatal exposure to a dam on metformin results in long-term programming of offspring weight, insulin secretion and intestinal microbiome.

Supported By: National Institutes of Health (K08DK102526)

2134-P

No Compensatory Increase in Non-β Hormone Expressing Cells in the Pancreatic Duct Glands in Type 1 Diabetes

SHWETA S. KULKARNI, MARK A. ATKINSON, ALEXANDRA BUTLER, Gainesville, FL, Doha, Qatar

Longstanding type 1 diabetes (T1D) entails a near total loss of β cells secondary to autoimmunity, fibrosis and decreased total organ mass, but accumulating evidence suggests there may be an endogenous attempt to regenerate β cells. Pancreatic duct glands (PDGs) represent a distinct anatomic compartment of the pancreas, forming blind ending outpouchings from the main pancreatic duct and its branches. The PDG is purported to be a potential stem/progenitor cell niche. PDGs respond to inflammation in T1D by becoming activated, evidenced by a high frequency of epithelial cell replication and an increase in progenitor-like cells. Hence, we addressed the hypothesis that in T1D, perturbation of hormone-expressing endocrine cells in the interlobular ducts (ILD) and PDGs exists. Pancreatic sections from sections 10 T1D (disease duration 8-58 year) and 11 similarly aged control (ND) donors were evaluated for replication and expression of known pancreatic endocrine hormones in ducts and PDGs. We confirmed increased duct and PDG replication in T1D (T1D vs. ND — ILD: 4.5 ± 1.8 vs. 0.8 ± 0.2%, p<0.05; PDG: 3.4 ± 1.3 vs. 0.4 ± 0.2%, p<0.05) and reduced frequency of insulin expressing cells (T1D vs. ND — ILD: 0.9 ± 0.4 vs. 4 ± 0.1%, p<0.01; PDGs: 0.08 ± 0.07 vs. 2.4 ± 0.6%, p<0.05). No differences were found in the frequency of other known endocrine cell types (T1D vs. ND — ILD: Glucagon: 1.5 ± 0.7 vs. 2.1 ± 0.6%, Somatostatin: 1.2 ± 0.4 vs. 1.6 ± 0.3%, Pancreatic Polypeptide: 0.4 ± 0.2 vs. 1.3 ± 0.3%, PDGs: Glucagon: 0.9 ± 0.9 vs. 1.6 ± 1.0%, Somatostatin: 1.9 ± 0.8 vs. 3.7 ± 1.9%, Pancreatic Polypeptide: 1.7 ± 1.1 vs. 2.1 ± 0.8%, p<0.05). All these data suggest that increased cell replication and the deficiency of insulin expressing cells in the PDG compartment of subjects with T1D are not associated with a corresponding increase in non-insulin hormone-expressing endocrine cells. Furthermore, the consistent observation of increased cell replication in the ducts and PDGs in T1D may implicate regenerative mechanisms towards an exocrine cell fate.

Supported By: National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases; JDRF, Network for Pancreatic Organ Donors with Diabetes

2135-P

Gli3 Regulates Pancreatic β-Cell Development in Part through Coordination with Other Islet Transcription Factors

DAVID SCOVILLE, Research Triangle Park, NC

Pancreatic β-cells play a central role in regulating glucose homeostasis. One prominent regulator of both β-cell fate and function is Gli3, a transcription factor with both co-activating and co-repressive roles. Both humans and mice lack a functional copy of Gli3. Interestingly, Gli3 is expressed relatively early during pancreas development prior to the differentiation of ductal and endocrine cells from a common lineage, and is maintained in both β-cells as well as ductal cells. Furthermore, postnatal deletion of Gli3 also results in hyperglycemia, suggesting Gli3 as a critical regulator of postnatal β-cell function as well. Yet, much is still known about the phenotype of Gli3 deletions, little is known about its molecular function.

My research focuses on how Gli3 regulates β-cell development and function. To determine which genes are regulated by Gli3, a mouse model with a pancreas-specific deletion of Gli3 was utilized. RNA-seq analysis of isolated islets revealed a large number of both upregulated and down-regulated genes, and ChIP-seq analysis of Gli3 in islets revealed many of these genes are direct targets of Gli3 regulation. Interestingly, Gli3 binding largely overlaps with binding of the transcription factor Nkx6.1, and partially overlaps with transcription factors Pdx1 and Nkx2.2, but shows less overlap with other islet-enriched transcription factors. This indicates that Gli3 could function in distinct regulatory complexes, and that better understanding of Gli3 gene regulation within the pancreatic β-cell will lead to a better understanding of how β-cell fate is controlled and maintained, and which genes are essential for postnatal function.

Supported By: National Institute of Environmental Health Sciences

2136-P

Effects of a Healthy Postweaning Diet on Endocrine Defects Caused By In Utero High-Fat Diet Exposure in Mouse and Japanese Macaque

JOSEPH ELSAK, PAUL KEVIT, ALVIN C. POWERS, MAUREEN A. GANNON, RITA BOTTINO, DIANA L. TAKAHASHI, Nashville, TN; Portland, OR; Pittsburgh, PA, Hillsboro, OR

The Developmental Origins of Health and Disease Hypothesis states that the in utero environment influences postnatal health and plays a role in disease etiology. In humans, exposure to maternal obesity in utero increases diabetes susceptibility in the offspring. In the U.S., it is estimated that about half of pregnancies occur in overweight or obese mothers. Thus, the consequences of maternal obesity will be manifested in future generations. Animal models have demonstrated that exposure to maternal high-fat-diet (HFD) feeding or obesity results in morphological alterations in the pancreatic islets, as well as impaired expression of islet transcription factors in the offspring. However, effects of in utero diet exposure often vary significantly between animal models. In a non-human primate (NHP) model of maternal overnutrition, we have demonstrated that fetuses exposed to HFD have reduced islet hormone transcript levels and increased β:α cell ratio due to decreased α-cell mass. This increase in β:α cell ratio persists post-weaning out to three years only when offspring are maintained on a HFD. However, maternal or post-weaning diet does not affect endocrine cell proliferation or β-cell mass in this model. Preliminary data in a mouse model of maternal overnutrition suggests that mice exposed to HFD are glucose intolerant shortly after weaning onto control diet, but have no differences in β-cell mass. When mice are aged to 12-weeks-old, the difference in glucose tolerance is no longer apparent, and body weight is not different between HFD-exposed and control mice. Data from the NHP model suggests that maternal HFD exposure results in subtle alterations in islet structure that persist only when offspring are maintained on HFD. In the mouse, impairments in glucose tolerance shortly after weaning are resolved when offspring are maintained on a control, lower-fat diet until 12 weeks of age.

Supported By: National Institutes of Health (2R01DK089984; U.S. Department of Veterans Affairs (I01BX003744)

2137-P

T3 and Glucose Increase Expression of ChREBPβ to Induce Expression of Phosphoehnopyruvate Carboxykinase (Pck1) Leading to Increased β-Cell Proliferation

LIORA S. KATZ, DONALD SCOTT, New York, NY

Thyroid hormone (T3) is required for islet development and function. Both T3 and high glucose concentrations are critical components of differentiation protocols of stem cells to β-cells. We previously demonstrated that in brown adipose tissue, T3 and glucose synergistically regulate carbohydrate response element binding protein (ChREBP), which in turn upregulates Ucp1, Glu4 and Fasn, resulting in increased thermogenesis, decreased body weight and improved glycemic levels. In the present study, we asked whether T3 and glucose signaling pathways can coordinately regulate transcription of genes important for β-cell function and mass. RNA-seq analysis was performed on cadaveric human islets from five different donors in response to low and high glucose concentrations (6 and 20 mM, respectively) and in the presence or absence of T3. We found that T3 and glucose coordinately regulate the expression of ChREBPβ and Pck1 (phosphoehnopyruvate carboxykinase-β). Typically, it is thought that Pck1 is not expressed in pancreatic β-cells, but it is a known target of T3 in hepatocytes. However, in FACS sorted adult human β-cells, we found that high concentrations of glucose (20 mM) and T3 (10 nM) induced the expression of Pck1 by 17±2.1 fold for mRNA levels. In addition, we found that overexpression of Pck1 together with its substrate dimethyl acetyl (DMA) increased β-cell proliferation in human islets (0.49±0.03% for human islets overexpressing Pck1, treated with DMM compared with 0.01±0.01% for control islets, n=4). Finally, using a sh-RNA knockdown approach, we demonstrated that in INS-1 cells, ChREBPβ is necessary for Pck1 dependent β-cell proliferation. V- and C-spacer analysis of the 3′ and glucose act together to regulate ChREBP which in turn upregulates expression of Pck1. In turn, Pck1 activity leads to increased β-cell mass.

Supported By: American Thyroid Association; Einstein-Mount Sinai Diabetes Research Center
Identification of Candidate Targets in Transcriptome of Islets from Offspring Exposed to High Glucose In Utero

JOSE CASASNOVAS, XI RAO, KOK LIM KUA, Indianapolis, IN

Offspring of diabetic mothers have higher risks to develop type 2 diabetes. Though exposure to hyperglycemia in utero is an inciting event, the mechanism by which it impacts insulin function and leads to increased risk of diabetes is unknown. We hypothesize that high glucose at late gestation alters pancreatic islet transcriptome during early life and impairs offspring islet function in adulthood. To test this, gestation day (GD) 20 fetal rats in left uterine horn were exposed to 48 hours of hyperglycemia (HG) by infusing 4mg/mL glucose directly into maternal left uterine artery. Right uterine pups remained euglycemic as internal controls (Con). On GD22, HG and Con pups were either euthanized or cross-fostered to healthy dams. Glucose tolerance testing was performed on weaning and at 2month old (2mo) offspring. Islets of GD22 and weanling pups were isolated for RNAseq. While pregnant dams and Con fetal pups remained euglycemic during infusion, HG pups had higher blood glucose (8±3 mg/dL vs. 5±1.5 mg/dL, p<0.05, n=20/20) and serum insulin levels (4.2±4.0 ng/mL vs. 3.0±0.6 ng/mL, p<0.05, n=6/6 pups). HG pups also had higher beta cell area (3±12% increase, p<0.05, n=5/5 pups) but lower neonatal blood glucose level (72±8 mg/dL vs. 129±20 mg/dL, p<0.05, n=9/12 pups). Subsequently, weaning and 2mo HG offspring had impaired glucose tolerance (55±23% higher iAUC, n = 8/10 pups, p<0.05). 2mo pups n=9/12 pups). Subsequently, weaning and 2mo HG offspring had impaired glucose tolerance following STZ treatment when compared to control mice. We hypothesized that mice with specific loss of Mig6 (β-KO and littermate controls with multiple low doses of STZ and RINs, SOPHIA SSDO, CHETAN POULEI, KARA M. MORTENSEN, MATTHEW J. MERRINS, Madison, WI, Cambridge, United Kingdom

The loss of insulin secretion is a hallmark of diabetes, and it is becoming clear that cell cycle regulators control insulin secretion as well as proliferation. It was recently reported that embryonic deletion of cyclin-dependent kinase 2 (Cdk2) in β-cells (Pdx1-Cre:Cdk2−/−) results in impaired glucose tolerance due to defective insulin secretion (Kim et al., J Biol Chem, 2017). Revealing a developmental or perinatal requirement of Cdk2. Here, we show that tamoxifen-inducible deletion of Cdk2 in adult β-cells [MIP-CreERT2:Cdk2−/−] enhances insulin secretion. Despite these differences, both models of Cdk2 deletion exhibited a strong increase in the glucose dependence of calcium oscillations. This effect is likely due to the loss of ATP-sensitive K₁₅ channels, since Kir6.2 transcript was reduced in Cdk2-null β-cells, and pharmacological inhibition of Cdk2 correspondingly reduced K₁₅ channel conductance. These results reveal that Cdk2 inhibits insulin secretion by limiting plasma membrane excitability via Kir6.2. In adult β-cells lacking Cdk2, we also observed a 45% reduction in depolarization-induced exocytosis, indicating that Cdk2 is required for the metabolic amplification of insulin secretion. Within the intermediary metabolic pathways, Cdk2-null β-cells exhibited reductions in glucose-dependent lactate accumulation, mitochondrial membrane potential, and mitochondrial NADH utilization. Together, these studies reveal that Cdk2 transcriptionally limits β-cell membrane excitability and the insulin secretory response, and is required to maintain proper metabolic function. Supported By: American Diabetes Association (16-16-212-212 to M.J.M.) National Institute of Diabetes and Digestive and Kidney Diseases (R01DK113103) National Institute on Aging (R21AG050353)

Impact of Mig6 on β-Cell Regeneration and Repair

BRANDON M. BAUER, KIMBERLEY EL, PATRICK T. FUEGER, Duarte, CA, Indianapolis, IN

Following autoimmune-mediated destruction of insulin secreting β-cells in type 1 diabetes (T1D), regenerative and repair pathways aim to restore β-cell mass and maintain euglycemia. However, these pathways are often unable to compensate for the loss of β-cell mass, resulting in insufficient insulin secretion and chronic hyperglycemia. Our lab previously demonstrated that this inability to compensate for the loss of β-cell mass may be at least in part due to mitogenic inducible gene 6 (Mig6), an anti-proliferative mechanism by which it impacts insulin function and leads to increased risk of diabetes. We hypothesize that high glucose at late gestation alters pancreatic islet transcriptome during early life and impairs offspring islet function in adulthood. To test this, gestation day (GD) 20 fetal rats in left uterine horn were exposed to 48 hours of hyperglycemia (HG) by infusing 4mg/mL glucose directly into maternal left uterine artery. Right uterine pups remained euglycemic as internal controls (Con). On GD22, HG and Con pups were either euthanized or cross-fostered to healthy dams. Glucose tolerance testing was performed on weaning and at 2month old (2mo) offspring. Islets of GD22 and weanling pups were isolated for RNAseq. While pregnant dams and Con fetal pups remained euglycemic during infusion, HG pups had higher blood glucose (8±3 mg/dL vs. 5±1.5 mg/dL, p<0.05, n=20/20) and serum insulin levels (4.2±4.0 ng/mL vs. 3.0±0.6 ng/mL, p<0.05, n=6/6 pups). HG pups also had higher beta cell area (3±12% increase, p<0.05, n=5/5 pups) but lower neonatal blood glucose level (72±8 mg/dL vs. 129±20 mg/dL, p<0.05, n=9/12 pups). Subsequently, weaning and 2mo HG offspring had impaired glucose tolerance (55±23% higher iAUC, n = 8/10 pups, p<0.05). 2mo pups n=9/12 pups). Subsequently, weaning and 2mo HG offspring had impaired glucose tolerance following STZ treatment when compared to control mice. We hypothesized that mice with specific loss of Mig6 (β-KO and littermate controls with multiple low doses of STZ and RINs, SOPHIA SSDO, CHETAN POULEI, KARA M. MORTENSEN, MATTHEW J. MERRINS, Madison, WI, Cambridge, United Kingdom

The loss of insulin secretion is a hallmark of diabetes, and it is becoming clear that cell cycle regulators control insulin secretion as well as proliferation. It was recently reported that embryonic deletion of cyclin-dependent kinase 2 (Cdk2) in β-cells (Pdx1-Cre:Cdk2−/−) results in impaired glucose tolerance due to defective insulin secretion (Kim et al., J Biol Chem, 2017). Revealing a developmental or perinatal requirement of Cdk2. Here, we show that tamoxifen-inducible deletion of Cdk2 in adult β-cells [MIP-CreERT2:Cdk2−/−] enhances insulin secretion. Despite these differences, both models of Cdk2 deletion exhibited a strong increase in the glucose dependence of calcium oscillations. This effect is likely due to the loss of ATP-sensitive K₁₅ channels, since Kir6.2 transcript was reduced in Cdk2-null β-cells, and pharmacological inhibition of Cdk2 correspondingly reduced K₁₅ channel conductance. These results reveal that Cdk2 inhibits insulin secretion by limiting plasma membrane excitability via Kir6.2. In adult β-cells lacking Cdk2, we also observed a 45% reduction in depolarization-induced exocytosis, indicating that Cdk2 is required for the metabolic amplification of insulin secretion. Within the intermediary metabolic pathways, Cdk2-null β-cells exhibited reductions in glucose-dependent lactate accumulation, mitochondrial membrane potential, and mitochondrial NADH utilization. Together, these studies reveal that Cdk2 transcriptionally limits β-cell membrane excitability and the insulin secretory response, and is required to maintain proper metabolic function. Supported By: American Diabetes Association (16-16-212-212 to M.J.M.) National Institute of Diabetes and Digestive and Kidney Diseases (R01DK113103) National Institute on Aging (R21AG050353)
The Increment of Noradrenergic Fibers Correlates with the Density of Dedifferentiated β Cells in Humans

FRANCESCA CINTI, ILENIA SEVERI, MARA SULEMAN, LORELLA MARELLI, PIERO MARCHETTI, SAVERIO CINTI, DOMENICO ACCILI, Rome, Italy, ANCONA, ITALY, FLISA, ITALY, NEW YORK, NY

β Cells dedifferentiation has been recently introduced as the main mechanism responsible for the functional "disappearance" of β cells from the islands of diabetic subjects. Starting from results obtained from a mouse model of type 2 (T2) diabetes (in whose a significant increase in density of noradrenergic fibers was detected compared to nondiabetic mice), we asked if the result could be replicated in humans and if it could be related to the process of dedifferentiation. Human pancreas of 8 healthy donors and 9 with T2 diabetes were analyzed by immunohistochemistry (M/F 4/4 vs. 5/4 NS; BMI (kg/m2) 24.8 ± 2.8 vs. 25.6 ± 4.1; NS). The dedifferentiation score was calculated as % of cells synaptophysin positive but negative for the four major pancreatic hormones. Tyrosine hydroxylase (TH) was used as a marker for the evaluation of noradrenergic fiber expression. The islands of diabetic subjects were about 3 times more innervated than controls (0.42 ± 0.51 vs. 1.66 ± 2.2 n.fibers/TH+island; p = 0.02); the increase of these fibers correlated positively with the dedifferentiation score (p <0.001; r = 0.69).

In conclusion, our data show an increase in the number of sympathetic nerve fibers potentially able to transmit inhibitory signals on insulin secretion in the islands of diabetic subjects. The important correlation with the dedifferentiation score suggests a significant role of noradrenergic fibers in the pathogenesis of the dedifferentiation process, introducing new strategies for the preservation of cellular mass/secreton and, therefore, for the prevention and treatment of T2 diabetes.

Tobacco Smoking Results in Reduced Pancreatic Islet Mass in Humans

MIKAËL CHEBOUN, JULIE A. KERR-CONTE, VALERY GMYR, DOROTHÉE THUILIER, RIDME EZZOUAOU, THOMAS HUBERT, VIOLETA RAVEROY, ANTONINO BONGIOVANNI, MEHDI DAOUDI, SR., MARIE-CHRISTINE VANTYGHEM, FRANÇOIS PATTOU, Lille, France

Epidemiological studies identify tobacco as an independent risk factor for T2D, however, the mechanisms involved remains unclear. Clinical studies incriminate an increase in insulin resistance but a direct effect on pancreatic islet mass is suggested by some animal studies. The aim of this study was to document the association between tobacco smoking and pancreatic islet mass in humans. Total islet mass (TIM) was measured in 484 pancreata from organ donors processed with standardized isolation technique for clinical islet transplantation. Number and size of islets were assessed following enzymatic digestion. Functional islet mass was estimated in a cohort of 845 obese subjects, by measuring c-peptide to glucose ratio at 30 min (CP/G-30) following an oral glucose load. Pancreatic islet mass proxies were correlated with donor smoking status and tobacco consumption (generalized linear model). TIM was negatively associated with smoking status in organ donors (estimate: -0.131; P = 0.017), independently of other known predictors: BMI (-0.019; P = 0.001), age (-0.009; P = 0.0001). CP/G-30 was also reduced in vivo in subjects with smoking history. TIM (Figures A-B) and CP/G-30 (Figures C-D) were negatively correlated with the level of tobacco consumption. Pancreatic islet mass was reduced in subjects with smoking history, with a dose-response relationship with tobacco consumption. Our results support the direct implication of smoking in T2D.

Identification and Analysis of a Novel Glucose Toxicity-Sensitive Gene in Pancreatic β Cell

NAKO SHIMO, TAKAAXI MATSUOKA, DAN KAWAMORI, SATOMI TAKEBE, TAKESHI MIYATSUKA, IICHIRO SHIMOMURA, SUITA, JAPAN, TOKYO, JAPAN

Chronic hyperglycemia in type 2 diabetes (T2D) causes pancreatic β-cell dysfunction, which is well known as glucose toxicity (GT), whereas the treatment of T2D improves that dysfunction. However, its underlying molecular mechanism has not yet been clarified. In this study, we aimed to identify and analyze a novel factor whose gene expression was altered by GT (GT-sensitive) and involved in β-cell function. For this purpose, type 2 diabetic db/db mice were treated with empagliflozin to selectively alleviate GT, as we recently reported (Shimo N, et al., 2019). Using the islet RNA from empagliflozin-treated (E) and untreated (U) mice, we performed DNA microarray analysis, and only 43 factors out of 33,779 probes showed more than two times as high signal levels in E as U. Among them, we focused on Tmem163, which is reported to be associated with T2D risk in GWAS and involved in the regulation of intracellular zinc levels. The Tmem163 mRNA expression levels in islets were significantly lower in U than normal control mice, and higher in E than U, which indicated that Tmem163 was GT-sensitive. The tissue distribution analysis by immunohistochemistry and immunoelectron microscopy revealed that Tmem163 was highly localized in pancreatic β-cells and accumulated in the membrane of insulin granule. Next, we found that Tmem163 knockdown significantly reduced glucose-stimulated and KCI-stimulated insulin secretion in MIN6 cells. In vivo, Tmem163 null mice (N) were comparable in body weight and blood glucose levels, but showed decreased glucose tolerance and insulin secretion in intraperitoneal glucose tolerance test, compared with wild type mice. Furthermore, the zinc content of islets in N tended to be lower than a hetero knockout mouse, suggesting a mechanism for β-cell dysfunction. These in vitro and in vivo findings suggest that the decreased expression of the novel GT-sensitive gene Tmem163 in islets causes the insufficient insulin secretion from pancreatic β-cells induced by chronic hyperglycemia.

Novel Use of Agent 11C-PHNO for Pet CT Imaging of Pancreatic Beta-Cell Mass

ELIZABETH SANCHEZ RANGEL, JASON BINI, NABEEL B. NABULSI, YIYUN HUANG, KEVAN C. HEROLD, ROBERT SHERWIN, RICHARD E. CARSON, GARY CLINE, NEW HAVEN CT

There is growing interest in developing a method to measure pancreatic beta-cell mass (BCM) so as to: 1.) monitor progression of beta cell changes in type 1 and type 2 diabetes; 2.) identify therapies to preserve, restore or regenerate beta cells; and 3.) monitor viability of islets after transplantation therapy. Given that beta cells and neurons have functional similarities, and beta-cell mass (BCM) so as to: 1.) monitor progression of beta cell changes in type 1 and type 2 diabetes; 2.) identify therapies to preserve, restore or regenerate beta cells; and 3.) monitor viability of islets after transplantation therapy. Given that beta cells and neurons have functional similarities,
we tested the hypothesis that receptors, transporters, or proteins essential for signal detection and propagation, may be common to both cell types. Hence, we assessed if Positron Emission Tomography (PET) imaging ligands originally developed for neuroimaging may provide a means for imaging BCM as well. Previous studies have shown higher uptake of 12C-1-(+)-4-propyl-9-hydroxyxanthozaxine (PHNO), a dopamine D2/D3 agonist radioligand (D3-prefering), in the pancreatic tissue of healthy controls vs. T1DM in humans. In this study, we sought to determine whether 11C-PHNO, would be useful for measuring BCM. Eleven subjects (6 with T1DM, 4 males and 2 females, age 30.8 ± 11.4 years, BMI 24.4 ± 2.0, and 5 matched healthy controls, 3 males and 2 females, age 32.2 ± 11.4 years, BMI 22.6 ± 2.1) underwent abdominal PET/CT imaging using 11C-PHNO. Regions-of-interest (ROIs) were applied to the pancreas, liver, spleen, and kidney and time-activity curves (TACs) were produced and converted to standard uptake value (SUV) units. The distribution of activity between the head, body, and tail of the pancreas was also assessed. We observed that there was a 41% reduction in 11C-PHNO SUV in T1DM patients as compared to the healthy control group (p = 0.026). Moreover, there was a positive correlation between plasma c-peptide concentrations and 11C-PHNO SUV in the pancreas (r = 0.78), although this relationship did not reach statistical significance (p = 0.1), most likely due to the small sample size. These data suggest that dopamine D3 expression in pancreatic tissue might serve as a useful biomarker for assessing beta cell mass in diabetic humans.

Supported By: National Institutes of Health

Liraglutide Inhibits Endoplasmic Reticulum Stress in Pancreatic Beta Cells via Regulation of the Homeodomain Transcription Factor Nkx6.1

YUKUN LI, YANAN DONG, LI SHILUN, PENG XUE, Shijiazhuang, China

The GLP-1 mitigates the endoplasmic reticulum (ER) stress in β cells. Nkx6.1 plays an important role in the development and survival of β cells. This study aims to investigate the relation of Nkx6.1 and liraglutide in the protective effect of endoplasmic reticulum stress in INS-1-3 cells. INS-1-3 cells were divided into different groups for treatment: control group, thapsigargin (TG)-treated group, TG and GLP-1 co-treated group. Knockdown of Nkx6.1 partially diminished protective effect of liraglutide. The cell viability and GSIS were decreased by 1.53 and 1.10 folds. These were associated with the suppression of the PERK, IRE1 and ATF-6 pathways. Knockdown of Nkx6.1 plays an important role in the development and survival of β cells. This study aims to investigate the relation of Nkx6.1 and liraglutide in the protective effect of endoplasmic reticulum stress in INS-1-3 cells. INS-1-3 cells were divided into different groups for treatment: control group, thapsigargin (TG)-treated group, TG and GLP-1 co-treated group. Knockdown of Nkx6.1 was established by lentivirus infection. RT-PCR was used to verify the expression changes of target genes. MTT and flow cytometry analysis were used to detect cell viability and apoptosis rates. Glucose stimulates insulin secretion (GSIS) was used to measure β cell function. In TG-treated cells, liraglutide significantly increased cell viability and GSIS by 1.53 and 1.89 folds. These were associated with the suppression of the PERK, IRE1 and ATF-6 pathways. Knockdown of Nkx6.1 partially diminished protective effect of liraglutide. The cell viability and GSIS were decreased by 24.7% and 54.0%. And both of the early and late apoptosis were increased by 1.55, 1.10 folds. Liraglutide protected INS-1-3 cells from TG-induced ER stress by suppressing the PERK, IRE1 and ATF-6 pathways. And its protective effects on ER stress was partially via transcription factor Nkx6.1.

**Figures 1-2.**

![Graph showing relative protein levels of CHOP, β-actin, TG, GLP-1, sCTRL, sNkx6.1](image)

**(2)** The protein levels of CHOP were measured by Western blot. *p*<0.05 compared with control and TG+L. **p**<0.05 compared with TG+L+sCTRL. (2)Differences in CHOP protein levels in different experimental groups.

2147-P

**Effects of Extra Virgin Olive Oil Polyphenols on Pancreatic Beta-Cell Function and Survival**

ANNALISA NATALUSCHIO, ROSARIA SPAGNUOLO, NICOLA MARRANO, GIUSEPPE PINA BIONDI, LUCIA DIPAOLA, ANGELO CIGNARELLI, SEBASTIO PERRINI, LUIGI LAVIOLA, FRANCESCO GIORGINO, Bari, Italy

Extra virgin olive oil (EVOO) is one of the major components of the Mediterranean diet and is appreciated worldwide because of its nutritional benefits in metabolic diseases, including type 2 diabetes. In addition to high levels of fatty acids, EVOO contains significant amounts of micronutrients such as polyphenolic compounds that may positively influence the metabolic status. In this study, we have evaluated the effects of such EVOO polyphenolic compounds on beta-cell function and survival. INS-1E cells were exposed to different doses (10-50-100 microM) of the main polyphenols of EVOO for 24 h. Under these conditions, glucose-stimulated insulin secretion (GSIS), insulin content, proinsulin mRNA expression and cellular apoptosis were evaluated. At the concentration of 10 microM, which is closest to that in EVOO, hydroxytyrosol, tyrosol and apigenin augmented proinsulin mRNA levels and insulin content; moreover, apigenin and luteolin enhanced GSIS. On the other hand, vanillic acid and vanillin were pro-apoptotic for beta-cells, even if they increased GSIS. Finally, ferulic and sinapic acids significantly worsened GSIS. Furthermore, although most of the polyphenol compounds at the concentration of 50 microM did not induce apoptosis, some of them (e.g., caffeic, vanillic and ferulic acids) caused a marked reduction in proinsulin gene expression. At the concentration of 100 microM, most polyphenolic compounds caused a reduction in proinsulin mRNA levels and enhanced apoptosis.

In conclusion, this study, comparing for the first time the effects of the main polyphenols contained in EVOO, shows that, at low concentrations, hydroxytyrosol, tyrosol, luteolin and apigenin exert positive effects on both the function and survival of beta-cells, suggesting that EVOO enriched with these compounds may improve insulin secretion and promote glycemic control in type 2 diabetic patients.

*Supported By: AGER 2 Project (2016-0174)*

2148-P

**Withdrawn**
**ISLET BIOLOGY—BETA CELL—STIMULUS-SECRETION COUPLING AND METABOLISM**

**2149-P**

**miR-204 Antagonim Enhances GLP-1 Receptor Function and Glucose Control**

Seonhio Jo, Jyunin Chen, Guanlan Xu, Truman Grayson, Lance Thielen, Anath Shalev, Birmingham, AL

Glucagon-like peptide 1 receptor (GLP-1R) is a G protein-coupled receptor that is highly expressed on pancreatic beta-cells and activated by endogenous incretins or anti-diabetic GLP-1R agonist drugs. GLP-1R function is important in maintaining glucose homeostasis and involves stimulation of glucose-induced beta-cell insulin secretion via cAMP generation. While GLP-1R expression has been shown to be downregulated in diabetes, the molecular mechanisms have not been fully elucidated. In this study, we have discovered that miR-204, a highly beta-cell-enriched microRNA that is upregulated in diabetes, directly targets the 3' UTR of GLP-1R and decreases its expression in INS-1 cells as well as primary mouse and human islets. Moreover, genetic knockout of miR-204 in vivo increased islet GLP-1R expression and enhanced GLP-1R agonist-induced cAMP production and insulin secretion, resulting in improved glucose tolerance as well as protection against diabetes. In addition, miR-204 antagonism was able to mimic the effects of genetic miR-204 deletion and resulted again in GLP-1R agonist-induced insulin secretion as well as improved glucose tolerance. Thus, these results indicate for the first time that GLP-1R is under the control of a micro RNA and suggest that antagonism-mediated inhibition of miR-204 represents a potential novel therapeutic approach to promote the actions of GLP-1R agonist drugs in a beta-cell-specific manner and thereby help treat diabetes.

**Supported By:** National Institutes of Health, JDRF

**2150-P**

**A Novel Mediator of Arsenic-Induced Pancreatic Beta-Cell Dysfunction**

Christopher M. Carmean, Nurhide Yokoi, Andrew G. Kirkley, Harumi Takahashi, Robert M. Sargis, Susumu Seino, Kobe, Japan, Chicago, IL

With up to 140 million people living above arsenic (I)S-contaminated groundwater, AS exposure presents a major health risk worldwide. Studies have revealed a positive correlation between AS exposure and diabetes, where those suffering from symptoms of chronic AS toxicity have 5-6 times the local rates of diabetes. Recent mouse models of AS exposure suggest that this form of diabetes may be mediated by pancreatic β-cell dysfunction.

To evaluate this possibility, the MIN6-K8 mouse β-cell line was utilized as a model. Three days of physiologically-relevant AS exposure decreased glucose-induced insulin secretion (GIS) without effects on basal secretion. Three days of exposure to 1 μM AS decreased GIS more than 80% without effects on cell count, total protein, total DNA, mitochondrial mass, or GSH/GSSG. RNAseq analysis of AS-exposed MIN6-K8 cells revealed 3 significantly regulated genes previously unassociated with β-cell function.

Each gene was individually knocked down by siRNA in the presence of AS. Knockdown of one of these genes, UDP-glucuronyltransferase 1αa (Ugt1a1αa), partially recovered GIS in AS-exposed cells. Ugt1a1αa is a phase 2 detoxification enzyme for the conjugation of small aromatic compounds.

The precursor and rate-limiting factor for serotonin production, 5-hydroxytryptophan (5-HTP), a known target of Ugt1a1αa and modulator of GIS, was decreased following AS exposure. Therefore, the AS-mediated increase in Ugt1a1αa expression may deplete serotonin, and secondarily 5-HTP, decreasing GIS. This work introduces a gene with a novel role in β-cell physiology and arsenic-mediated pathology.

**Supported By:** American Diabetes Association (17-17-IBS-212 to M.J.M.); National Institute of Diabetes and Digestive and Kidney Diseases (R01DK101683, RO1DK113013); National Institute on Aging (R21AG050135)

**2151-P**

**Impaired Glucagon and Insulin Responses in Mice Lacking the Cl- Loader Nkcc2a**

Lisa E. Kelly, Mauricio Difuvillo, Dayton, OH

In pancreatic β-cells, glucose metabolism and plasma membrane depolarization are accountable for the early secretory response, a mechanism regulated primarily, though not exclusively, by ATP-sensitive K+ channels. In most cells, including β-cells, the net functional balance between Cl- load- ers e.g., Nkcc1 and Nkcc2a and excluders like Kcc2 keeps the intracellular Cl- concentration above equilibrium creating an outwardly directed anionic gradient, which is electrogenically dissipated by Cl- channel opening. This makes possible the additional driving force for depolarization, which in β-cells prolongs the action potentials necessary for sustained insulin secretion. β-cells express low levels of the ‘kidney-specific’ Na+-K+Cl- transporter Nkcc2a. This protein and Nkcc1 are targeted by bumetanide, which by blocking Cl- loading into β-cells, impairs insulin secretion provoking intermittent hyperglycemia, as seen in patients treated with this diuretic. Since the chronic functional implications of Nkcc2a in fuel homeostasis in vivo remain unexplored, we subjected Nkcc2a−/− mice to dynamic tests of glu- cose homeostasis and determined their secretory responses in vivo and in vitro using islets. We found that Nkcc2a−/− mice exhibit: i) increased steady-state blood glucose, plasma insulin, glucagon and de novo hepatic glucose production, ii) absent glucagon responses to physiological (0h) or prolonged (16h) fasting, iii) glucose intolerance and delayed in vivo insulin responses to glucose, iv) hyperplastic and hypertrophic α- and β-cells, v) increased islet insulin responses to glucose, and vi) normal and reduced expression levels of Nkcc1 and Kcc2, the main Cl- loader and excluder in β-cells, respectively. Together, our results suggest for the first time that mice lacking Nkcc2a exhibit a complex metabolic phenotype related to unrestrained plasma glucag, impaired insulin and glucagon responses in vivo in spite of compensatory mechanisms related to the regulation of Cl- transport in the islet.

**Supported By:** American Diabetes Association (17-17-IBS-212 to M.J.M.);

**FSTL3 Inhibition Restores Glucose Responsive Insulin Secretion in Nonfunctional Human Islets**

Alan Schneyer, Melissa Brown, Concord, MA, West Hartford, CT

Type 2 diabetes results from inadequate insulin production to control blood glucose. To address this need for replacing lost insulin-producing beta cells, most therapeutic development strategies are focused on enhanc- ing functional beta cell number. Fairbanks Pharmaceuticals is pursuing therapies that enhance beta cell function and regeneration and is based on prior research in which inactivation of follistatin-like-3 (FSTL3) resulted in enlarged islets, increased beta cell number, and enhanced insulin secretion. At least some of these new beta cells arose from alpha to beta cell transdifferentiation in FSTL3 knockout mice. Fairbanks has produced a monoclonal antibody (FP-101) that can completely block FSTL3 from binding activin A and B, GDF11, and myostatin that could also disrupt pre-formed and oth- erwise irreversible complexes. FP-101 was also able to restore glucose-
responsive insulin secretion in otherwise non-functional islets taken from HFD-fed mice. To determine if FSTL3 neutralization could be effective in humans, human islets from normal donors were first exposed to elevated glucose (25 mM) for 48-72 hours, a commonly utilized model for glucotoxicity. As expected, this caused loss of glucose response to subsequent GSIS. However, when treated for 24 hours with FP-101, GSIS was restored, indicating that neutralization of FSTL3 might be an effective strategy for restoring function to human non-functional islets. This observation agrees with previous research in which activin treatment directly restored GSIS in human islets from diabetic donors. Taken together with the potential for induction of alpha to beta cell transdifferentiation, these results suggest that neutralization of FSTL3 may have a dual benefit with acute restoration of GSIS in non-functional islets and chronic treatment leading to restoration of beta cell number through enhancement of alpha to beta cell transdifferentiation. In vivo studies will be initiated shortly.

Supported By: National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases (R43DK107018-02 to A.S.)

2156-P

Insulin and Glucagon Interaction Studied by Separate and Combined Receptor Antagonism

KATRINE D. GAIL SGAIJRD, JENS J. HOLST, MARIE WINTHER-SORENSEN, NICOLAI J. WEVER ALBRECHTSEN, JENS PEDERSEN, Copenhagen, Denmark

Insulin and glucagon are mutually influencing not only the actions of each other but also the secretion, which makes it very complicated to unravel their roles in integrated metabolism. Having studied in detail the actions of glucagon receptor antagonism in mice, we decided to also study the effects of insulin receptor antagonism and their combination. Female C57BL/6J mice (n=72) were administered an insulin receptor antagonist (IRA) (SIBII, 30 mmol/kg), a glucagon receptor antagonist (GRA) (25-264, 100 mg/kg), or both IRA and GRA (IRA+GRA) three hours before intravenous administration of saline, glucose (0.5g/kg) or amino acids (1 μmol/g) (both antagonists were generous gifts from Novo Nordisk A/S). As expected, IRA caused hypoglycemia (15.6±1.0 mM vs. 8.4±0.3 mM, P<0.0001) and hyper-insulinemia (51.67±3.44 ng/mL vs. 0.72±1.19 ng/mL, P<0.0001) at fasting, but reduced glucose-induced inhibition of glucagon secretion ([AUC]0-114.0±24.0 min × pM vs. [AUC]0-211.8±10.4 min × pM, P<0.0001). GRA treatment resulted in mild hypoglycemia (P=0.03), hyperglucagonemia (P=0.04), and did not influence insulin secretion (P=0.9) at fasting. However, after administration of both IRA and GRA, insulin secretion was significantly reduced (91.3±3.0 mU/L vs. 51.07±3.44 ng/mL, P<0.0001), finally, GRA+IRA administration resulted in blood glucose concentrations equal to those of vehicle treated mice upon a glucose challenge ([AUC]0-20 min = 342.7±29.3 mmol × min vs. 353.1±39.1 mmol × min, P=0.8).

In conclusion, using both glucagon and insulin receptor antagonists, it can be demonstrated in mice that both hormones are essential for the maintenance of fasting glucose metabolism and that the secretion of both is regulated by powerful negative feedback mechanisms. Insulin contributes to glucose-induced inhibition of glucagon secretion, while glucagon has a positive effect on insulin secretion.

2157-P

Canagliflozin Improves Glycemic Control and Beta-Cell Mass in the TallyHo Polygenic Model of Type 2 Diabetes

IUJOLANA POPESSLU, GEORGE M. MUSSIMAN, COREY B. HUGHES, TERRANCE J. JANE, JR., PHIL RAY, CLAY BURN, JOHN FOWLES, KATHRYN M. THAIRKILL, Lexington, KY

SGLT2 inhibitors reduce insulin resistance and may improve beta-cell function in humans with T2D. We studied the effects of Canagliflozin (Can) on glucose homeostasis, islet architecture and endocrine cell fate in male TallyHo/Jng (TH) mice, a new model of T2D, which mimics many aspects of polygenic T2D in humans. By 8 weeks of age, all TH mice developed moderate-obesity and hyperglycemia compared to control SWR/J mice; ~60% of TH mice converted quickly to overt diabetes, characterized by elevated BG values (~400mg/dL [Hb] mice), while the remaining cohort maintained lower BG levels.

Supported By: National Natural Science Foundation of China (8170772)
was to identify proteins that are important regulators of GLP-1 receptor agonist (exendin-4), cAMP, and potassium-induced insulin secretion. By using this methodology, complement-1q-like-3 (C1ql3) was identified and gene enrichment based analyses were performed to determine cellular miRNA, islets from lean and obese mice were analyzed to identify candidate microRNAs. Microarray data from multiple tissues including liver, adipose, gastrocnemius, and islets, islets from lean and obese mice, suggesting improved beta-cell function by C1ql3. Immuno-fluorescence staining for islet hormones showed that, compared to untreated animals, C1ql3 re-established the islet area and the beta-cell number/islet in HG mice (possibly due to reduced apoptosis of beta-cells), in addition to decreased number of alpha- and delta-cells/islet. In HG/Cana mice, the majority of insulin+ cells expressed the glucose transporter Glut2, while its expression was undetectable in insulin+ cells of the HG/ Chow mice, further suggesting an improvement in glucose sensing capability of beta-cells with Cana treatment. Our study shows that C1ql3 has beneficial effects on preserving beta-cell mass, identity and function in a model of early-onset T2D.

Supported By: National Institutes of Health (5R21AR070620-02)

2158-P

Mechanisms Underlying the Progressive Loss of Beta-Cell Function and Mass in Neonatal Diabetes Are Reverted by Dagapilofzin Therapy

ZEE NAT A. SHIRY, ZIHAN YAN, ALESSANDRO USTONE, MARIA S. REMEDI, St. Louis, MO

Progressive loss of beta-cell function and mass are classic findings in diabetes, and are frequently attributed to membrane hyperexcitability, insulin hypersecretion and beta-cell death. However, we demonstrated that in an insulin secretion-deficient mouse model of human neonatal diabetes (K_{ATP}-GOF), loss of beta-cell mass still occurs in the absence of these factors. To study the underlying mechanisms of it, we performed experiments on day 7, 15, 22 and 30 post-disease induction. While K_{ATP}-GOF mice are hyperglycemic by day 7, insulin content is maintained at control levels. Surprisingly however, there is a dramatic decrease in insulin content at day 15, accompanied by augmented proinsulin/insulin ratio, altered calcium dynamics and increased oxidative and ER stress. We hypothesized that this is induced by hyperglycemia, and not by lack of insulin; and that lowering blood glucose alone will be sufficient to prevent loss of beta-cell mass and improve function. K_{ATP}-GOF mice were treated with dagapilofzin, a sodium-glucose transporter-2 (SGLT2) inhibitor clinically used to reduce blood glucose by preventing renal glucose reabsorption. Dagapilofzin significantly reduced blood glucose by increasing urinary glucose excretion without changing circulating insulin levels. Dagapilofzin therapy (10 days) marked improved insulin content, reduced proinsulin/insulin ratio and enhanced beta-cell function by alleviating oxidative and ER stress. Together, we demonstrate that beta-cell failure and loss of beta-cell mass is induced by increased oxidative and ER stress in a reversible manner, and that normalization of blood glucose alone is sufficient to prevent/revert the progressive beta-cell dysfunction and failure, opening the exciting possibility of prevention of diabetes progression.

Supported By: National Institutes of Health (2U2XDK108472 to Z.A.S., DK098584 to M.S.R.)

2159-P

The Complement-1q-Like-3 Inhibits Insulin Secretion by an Adhesion G-Protein Coupled Receptor, BA13 in Pancreaticbeta Cells

RAJESH GUPTA, MIKE SCHAUD, MICHELLE E. KIMPLE, JAMES E. KOLTES, Birmingham, AL

Aims: The complement-1q-like-3 (C1ql3) is important for beta-cell function and mass in response to low and submaximal concentrations of glucose, fatty acids, amino acids, and mitochondrial metabolites. We further observed that the expression of BA13, a receptor for C1ql3, is elevated in islets of obese compared to lean mice. Knockdown of BA13 in beta-cells increased glucose-stimulated insulin secretion by 2-fold and soluble C1ql3-binding fragment of BA13 completely blocked the inhibitory effects of C1ql3 on cAMP-stimulated insulin secretion. These findings report the identification of a novel pathway in C1ql3/BA13 that antagonizes GLP-1/cAMP signaling to inhibit insulin secretion from beta-cells. We propose that the activation of C1ql3/BA13 signaling contributes to type 2 diabetes and may offer therapeutic alternatives to treat type 2 diabetes.

Supported By: American Diabetes Association (1-T8-PDF-103 to R.G.), National Institute of Diabetes and Digestive and Kidney Diseases (R00DK59575-03 to S.B.), University of Alabama (P30DK079632 to S.B.)

Newly Revealed Role for OGT in Obesity-Precipitated Beta-Cell Hyperinsulinemia

AMBER D. LOCKRIDGE, SEOKWON JO, NIKLAS E. DAMBERG, RAKUMUNAR MOHAN, EMILYN ALEJANDRO, Saint Paul, MN, Minneapolis, MN

Highly expressed in the beta-cell, the nutrient sensor O-GlcNAc transferase (OGT) couples metabolic environment to cellular behavior through dynamic protein modifications (O-GlcNAcylation) but the role of OGT in beta-cell hyperinsulinemia is unknown. Here, we observed changes in OGT -deficient pancreatic islets and mouse models of obesity-induced diabetes. In a mouse model of partial beta-cell OGT loss, we found that Rip-Cre, OGT+/-, (OGT Het) mice failed to develop hyperinsulinemia over 12 weeks of HFD. Only Het islets isolated from HFD mice showed deficits in stimulated insulin secretion (30 mM KC), HFD OGT t/+). Nutrient-damaged ATP was not impaired, but islets with full beta-cell OGT KO (Rip-Cre, OGT t/-) showed no acute secretory potentiation to palmitate (100 μM) implicating the amplification arm of the stimulus-secretion pathway. HFD beta-cell mass was similar (OGT Het vs. WT) but increased Ins+/Gcg+ cells and Ngn3 gene expression in OGT Het islets suggested functional beta-cell loss through enhanced dedifferentiation. HFD hyperinsulinemia was reinitiated in a tamoxifen-induced OGT loss model (Rip-Cre, OGT t/-), which also showed elevated proinsulin/insulin serum ratios (6 weeks HFD). Transcriptome analysis by RNA-sequencing of OGT KO and WT mouse islets revealed differential gene expression of proteins involved in membrane depolarization (Kcnj11, Abcc8),
ER calcium (Atp2a2), lipid uptake (lip) and β-cell differentiation (Lhx3). An upstream analysis suggested impairments in free radical scavenging, supported by elevated levels of 4-HNE lipid peroxidation staining in post-HFD OGT HET islets. However, antioxidant supplementation of HFD chow (0.2% alpha-lipoic acid) did not rescue OGT HET in vivo deficits. These data reveal OGT as a critical mediator of β-cell adaptation to diet-induced obesity. Our data highlight protein O-GlcNAcylation as a potential therapeutic target to prevent prediabetic progression.

Supported By: National Institutes of Health

**ISLET BIOLOGY—SIGNAL TRANSDUCTION**

**2162-P**

**Synchronized Microfluidic System to Dynamically Assess Pancreatic Islet Function beyond Glucose-Stimulated Insulin Secretion**

STEPHAN NIEUWOUTD, RUTH MCDOWELL, HUI ZHANG, JOHN P. KIRWAN, Cleveland, OH

The endocrine function of pancreatic islets goes beyond glucose stimulated insulin secretion (GSIS). Besides glucose, dynamic regulation through a variety of incretin hormones, drugs, and metabolites have been shown to modulate insulin secretion. The most commonly applied ex vivo and in vitro methodologies to study islet function are static in nature; carried out in standard well formats for extended incubation times. This approach ignores the dynamic nature of secretion and regulation thereof, and limits the complexity of scientific questions that may be posed. In the last decade several groups have begun using microfluidic devices to assess islet function in a dynamic environment, which aims to mimic a physiological bolus of glucose followed by imaging and secretory analysis. Thus far no commercial research device has been made available to the scientific community, requiring the in-house development of microfluidic islet analysis systems by groups aiming to take a more in-depth view of pancreatic islet function. We have developed a fabrication processes for poly-methyl methacrylate (PMMA) microfluidic chips, with micromilled channels and pockets into which islets will be hydrodynamically trapped. These optically clear chips allow for direct fluorescent imaging of the trapped islets, with real-time calcium flux (Fura-2-AM) and mitochondrial potential (Rhodamine 123) assays. Using the FC (Inter-Integrated Circuit, NXP Semiconductors) protocol, we are able to synchronize several microcontrolled syringe pumps (and a fraction collector) to produce precise concentrations of glucose, hormones, metabolites, and factors of interest in a time-dependent manner. This system has applications in our study of the effects of bariatric surgery (in rodents) on pancreatic islet function, as well as the mechanisms by which myokinins may directly regulate pancreatic endocrine function.

**2163-P**

**Diminished Ca2+ Signaling, Ca1 Channel Expression, and Activity in Pancreatic Beta Cells Expressing Mutated DISC1 (Disrupted in Schizophrenia 1)**

PING LU, ROHIT B. SHARMA, LAURA C. ALONSO, RONGHUA ZHUO, ANN R. RITTENHOUSE, AGATA JURZCYK, Worcester, MA

In addition to cognitive impairment, schizophrenics often suffer from non-obese T2D. Here, we examined whether similar cellular changes occur in pancreatic beta-cells as found in neurons from a genetic model of schizophrenia. Specifically we tested whether beta-cells exhibit disrupted excitation-secretion coupling when a truncated human DISC1 (thDISC1) gene, originally discovered in a Scottish family having high penetrance for schizophrenia, is expressed selectively in mouse beta-cells upon ingesting doxy-cycline (dox). Expression of thDISC1 significantly decreases blood insulin levels and GSIS from isolated mouse islets, revealing an independent role for DISC1 in beta-cells. In central neurons, DISC1 regulates Ca2+ Ca1 channel expression, Ca1 infux and transmitter release. To determine whether DISC1 similarly regulates Ca1 physiology in beta-cells, we tested thDISC1 DX/DX vs. DX-ca1 beta-cells for changes in intracellular Ca1-signalizing using Fura-3; AM; ii) Ca1 channel expression, the dominant channel class controlling GSIS; iii) and Ca1 channel activity using whole-cell recording methods. We found increases in Ca1 following 20 mM glucose were delayed ~3 min and diminishing ~50% in dissociated beta-cells expressing thDISC1. When sections of pancreas were stained with an anti-Ca1.2/1.3 antibody, thDISC1 DISC1 DX/DX vs. DX/DX insulin-positive cells exhibited decreased staining. Lastly, both peak inward Ba2+ current and FPL 64176 induced long-lasting L-type tail current decreased significantly in thDISC1 DX/DX vs. DX/DX beta-cells. No obvious change in activation kinetics was observed. These changes in excitation-secretion coupling parallel those in neurons expressing truncated DISC1. Thus at the cellular level, truncated DISC1 precipitates disorders of secretion such as schizophrenia and T2D.

Supported By: Diabetes Research Council

**2164-P**

**Glucagon Expression Is Regulated by Exendin-4 via CaMKK/AMPK/FoxO1 Pathway in Alpha TC1.6 Cells**

JINGYA LYU, HITOMI IMACHI, KENSUKE FUKUNAGA, SEIYUKI SATO, TAD DONG, TOMOHIRO IBATA, TOSHIHIRO KOBAYASHI, KOJI MURAO, Kagawa, Japan

Exendin-4, as an analogue of glucagon-like peptide-1, is currently used for the treatment of type 2 diabetes by enhancement of glucose-induced insulin secretion. Preliminary studies showed that secretion of glucagon is inhibited by exendin-4 in vivo and in vitro. However, the detailed mechanism in exendin-4 regulated glucagon expression is not clear. In this study, we firstly proved that exendin-4 decreased the mRNA and protein expression of glucagon in a dose-dependent manner. Following, the promoter activity of glucagon was significantly decreased by exendin-4 and inhibition of Ca2+/calmodulin-dependent protein kinase kinase (CaMKK) signaling pathway by its specific inhibitor, STO-609 rescued this effect. Since glucagon secretion is regulated by AMP-activated protein kinase (AMPK) and AMPK is able to be activated by CaMKK, we checked the role of AMPK in this process and found exendin-4 activated AMPK at Thr172 site. Additionally, inhibition of AMPK activity by its specific inhibitor or overexpression of domain-negative AMPK canceled the effect of exendin-4 on glucagon promoter activity. As activation of AMPK enhances FoxO transcriptional activity, to further study the transcription of glucagon, we used ChIP assay to demonstrate that transcription factor FoxO1 could bind to glucagon promoter region and exendin-4 decreased glucagon expression via down-regulation of FoxO1. Mutation of FoxO1-binding site in glucagon promoter or silence of FoxO1 canceled the effect of exendin-4 on glucagon expression.

In summary, our results proved that exendin-4 decreases the expression and transcription of glucagon via CaMKK/AMPK/FoxO1 pathway in pancreatic alpha cells, contributing to new knowledge about the regulation of glucagon gene by exendin-4.

**2165-P**

**Generation of Insulin Expressing Cells in Mouse Small Intestine by Pdx1, MafA, and BET2/NeuroD**

LEE JO HYUN, JINWON KIM, KUN-HO YOON, Seoul, Republic of Korea

To develop the beta-like cells for diabetes therapy, adult stem cells have been identified in various tissues and studied for their conversion into beta cells. Pancreatic progenitor cells are derived from the endodermal epithelium and formed in a similar manner as gut progenitor cells. Here, we generated insulin-expressing cells from the intestinal epithelial cells that induced many of the specific pancreatic transcription factors using adenoviral vectors carrying three genes: Pdx1, MafA, and BET2/NeuroD (PMB). By direct injection into the whole intestine, adenosviruses (Ad) were successfully delivered to the intestine. After virus injection, we could confirm that the small intestine of the mouse was appropriately overexpressed with the Ad-Pdx1 and triple Ad-PMB. Four weeks after the injection, insulin mRNA was expressed in the small intestine, and the insulin gene expression was induced in Ad-Pdx1 as well as Ad-PMB compared to control Ad-GFP. In addition, the conversion of intestinal cells into insulin-expressing cells was detected in parts of the crypts and villi located in the small intestine.

In conclusion, these data indicated that Pdx1, MafA, and BET2/NeuroD facilitate the differentiation of mouse intestinal cells into insulin-expressing cells. The small intestine is an accessible and abundant source of surrogate insulin-producing cells.

**2166-P**

**Evaluation of CFTR Expression and Localisation in Human Pancreas**

RASHMI R. MAHESHWARI, CLAIRE J. JONES, JAMES A.M. SHAW, MICHAEL G. WHITE, Newcastle upon Tyne, United Kingdom

Introduction: Cystic fibrosis-related diabetes (CFRD) is the most common co-morbidity in people with CF, occurring in 40-50% of adults. Whilst it is established that CFβ-cell dysfunction in cystic fibrosis (CF) leads to diabetes, the mechanism by which the CF transmembrane conductance regulator (CFTR) channel influences insulin secretion remains debated. Currently, three major hypotheses have been proposed: 1. Intrinsic CFTR-dependent pathways of insulin secretion 2. Pancreas-extrinsic CFTR defects 3. Remodeling of islets following loss of exocrine tissue due to inflammation. Since the contribution of each to the pathogenesis of CFRD remains largely unknown, we sought to determine CFTR localisation within human pancreas using novel and highly sensitive approaches.
Methods: Expression of chromogranin A (ChnA), CTRF and keratin 19 (K19) was assessed by immunofluorescence (IF) staining of obtained tissue from deceased donors without diabetes (n=10, age: 23-71 years). Two CTRF antibodies (a6576 and a6590) obtained from the CF Foundation were used to confirm specificity, with ductal and endocrine cells determined by K19 and ChnA respectively. CTRF RNA expression was determined by RNAseq® in situ hybridization (ISH) and combined with either ChnA or insulin immunohistochemistry (IHC).

Results: IF staining of pancreatic tissues indicated co-localisation of CTRF in K19 ductal cells, but not in ChnA endocrine cells. These observations were confirmed by combined RNAseq® ISH and IHC (ChnA and insulin), which demonstrated the absence of CTRF RNA in human islets.

Conclusion: Employment of these highly sensitive techniques has demonstrated absence of CTRF within normal β-cells or any other islet endocrine cell types. This is in line with recent observations in isolated human islets. We conclude that CTRF abnormalities do not directly impact beta-cell function and that CTRF is mediated by factors extrinsic to the pancreatic endocrine compartment.

Supported By: Cystic Fibrosis Trust

2167-P

Hyperproinsulinemia in OGlcNAc Transferase Deficient Mice Is Associated with Loss of CPE and elf4G1, but -Cell Deletion of elf4G1 Induces Glucose Intolerance Independent of CPE Dysregulation

SHERMAN, J.; AMBER J. LOCKRIDGE, EMILYN ALEJANDRO, Minneapolis, MN, Saint Paul, MN

β-cell loss of OGlcNAc transferase (JOGT), the sole enzyme that adds OGlcNAc post-translational modification onto target proteins impacting their function and stability, leads to diabetes and islet failure in mice. (JOGTKO) mice present hyperproinsulinemia, typified by increased serum proinsulin/insulin ratio. Here, we show that (JOGTKO) islets have reduced carboxypeptidase E protein but not mRNA (CPE, an exopeptidase that converts proinsulin to insulin), independent of sex, and glucose levels. We identified that CPE is neither the target nor a binding partner of OGt, Eukaryotic initiation factor 4 gamma 1 (elf4G1), previously shown to regulate CPE in vitro, is reduced at the protein level, but not mRNA, in (JOGTKO) islets. We identified that elf4G1 is OGlcNAc-modified in β-cells and mutation of the putative OGlcNAc site at serine 61 to alanine led to decreased protein stability, but not CPE translation. To assess the role of elf4G1 on CPE regulation in vivo, we generated mice with β-cell specific deletion of elf4G1 (RIPCre; elf4G1fox/xβ(JOGTKO)), in R12δH elf4G1 (elf4G1β) background. At 6 weeks of age in normal chow diet, glucose intolerance was evident between (JOGTKO) and littermate control elf4G1 mice, without alteration in peripheral insulin sensitivity. Surprisingly, no apparent insulin processing defect was observed between elf4G1KO and elf4G1β mice, consistent with the observed normal level of CPE protein among islets of elf4G1 KO, elf4G1 or wild type mice via immunofluorescence, and comparable serum proinsulin/insulin ratio in elf4G1KO and elf4G1β mice. Significant reduction in the average β cell size and increased number of α cells was evident in elf4G1KO vs. elf4G1β mice, hinting at loss in β cell mass. Together, these data unveil the regulation of OGt on elf4G1, and underscore the novel role of elf4G1 on glucose homeostasis and modulation of β cell size.

Supported By: National Institutes of Health

2168-P

Quantitative Proteomic Analysis on Human Islets—New Markers of Cellular and Metabolic Dysfunction

CHIARA MARIA ASSUNTA CEFAIO, TERESA MEZZA, ROHIT KULKARNI, ANDREA GIACCA, Rome, Italy; Boston, MA

The pathogenesis of type 2 diabetes is characterized by a progressive β-cell dysfunction resulting in both quantitative and qualitative loss of insulin secretion. However, the molecular mechanisms underlying this progressive functional loss are still unknown. The aim of the study is to highlight β-cell dysfunction resulting in beta-cells by examining expression responses of miR-199a precursors genes (primiR-199a1, a2 and b) and its mature forms (miR-199a-3p and -5p) and promoter transcriptional activity assays in mouse islets and mouse insulinoma (MIN6) cells treated with different stimuli. We found that islets from male and female mice equally express the mature miR-199a-3p and -5p. However, the primiR expression is different: while primiR-199a1 expression is 2-fold greater than primiR-199a2, primiR-199b is barely detected in mice islets. The same primiR expression profile was found in MIN6 cells except that only the mature miR-199a-3p is expressed. A 2-fold increase in primiR-199a1 and -a2 mRNA levels was observed by 24 h culture of mouse islets in high glucose compared to 5.5 mM. Similar responses to high and low glucose were observed in MIN6 cells as early as 6 h. Interestingly, 30 mM of KCI treatment was sufficient to prevent the low glucose-induced decline in primiR-199a-a2 expression but not in 199-a1 in MIN6 cells, indicating that cali-
Islet Biology—Signal Transduction

Endocannabinoid Receptors Activity Modifies Insulin Secretion in Response to Glucose Exposition

ALONSO VILCHES-FLORES, GUADALUPE M. GARCIA-LUNA, Mexico City, Mexico

Background: Recent studies suggest the participation of the endocannabinoid system in the development of type 2 diabetes mellitus, involved with the regulation of physiological and metabolic processes. The endocannabinoid system is expressed in pancreatic islets and presents a key role in gene expression and regulation of pancreatic hormones secretion. In type 2 diabetes patients and in obesity the blood levels of endocannabinoids are increased, however, little is known about the mechanisms of action in islets and its relation with glucose in media.

Methods: Isolated pancreatics islets of mouse were incubated for 24 hours at 5.5mM and 15mM glucose concentration, in the presence of anandamide or THC as cannabinoide receptors agonists, or with antagonist AM251. Glucose-stimulated insulin secretion and intracellular cAMP were analyzed by EUSA and cytosolic calcium changes were measured by spectrofluorometry with FURA-2.

Results: Activation of endocannabinoid receptors significantly increases cAMP levels at low glucose concentration, meanwhile no further changes were observed at high-glucose concentration, correlated with a similar effect in insulin secretion. Short-time exposure to the antagonist decreases insulin secretion under both glucose conditions. Anandamide does not induce changes in intracellular calcium but THC decreases it at high glucose concentration. Antagonist AM251 enhances calcium fluctuations, suggesting an indirect modulation of insulin secretion.

Conclusions: Endocannabinoid receptors modulation regulates intracellular mechanisms involved in insulin secretion, according to glucose exposure, in isolated pancreatic mouse islets.

Towards Generating Spatiotemporal Multiscale Models of Human Pancreatic Beta Cells

KATE L. WHITE, KYLE MCCLARY, JITIN SINGLA, RAYMOND C. STEVENS, Los Angeles, CA

Diabetes is a worldwide problem affecting hundreds of millions of people with increasing patient numbers every year. Our goal is to assemble a spatiotemporal, multi-scale (atomic to cellular) model of a human pancreatic β-cell to gain a more holistic understanding of β-cell function in diabetes. This effort requires the convergence of structural biology, electron microscopy, X-ray tomography, -omics, live cell imaging, computational and integrative modeling, systems biology, and digital arts. To best integrate these approaches, we formed a consortium of leaders in each field to help collect the necessary data for assembling such a model. As a first step, we have characterized the cellular ultrastructure and generated a consensus of the components of a cell (proteins, nucleic acids, metabolites, lipids, etc.). Two important aspects of this project are developing new tools for data integration and improving communication between collaborators in distant fields. To achieve this goal, we are collaborating with the USC School of Cinematic Arts to generate a virtual reality experience of a β-cell that serves as a new type of tool that can toggle between experimental techniques and scales. This immersive model will allow researchers, students, and the public to explore the rich biochemical world of a β-cell. Together, these models will represent a sophisticated convergence of our understanding of cellular structure and function, revolutionizing biological discovery, open new dimensions of research, and accelerate advancements in healthcare.

Supported By: University of Southern California

Exploring the Role of Calcium-Activated Potassium Channels in Alpha-Cell Function

MATTHEW DICKERSON, MOLLY K. ALTMAN, PRASANNA DADI, NICHOLAS C. VIERRA, DAVID JACOBSON, Nashville, TN, Davis, CA

Calcium influx into pancreatic α-cells through voltage-dependent calcium channels (VDCCs) is required for glucagon (GCG) secretion and the mechanisms that mediate this process become defective during the pathogenesis of diabetes. Potassium channels are key regulators of membrane potential (V_m) and thus, modulate VDCC activity. However, the role of calcium-activated potassium (KCa) channels in α-cell calcium handling and GCG secretion have not been determined. The aim of this study was to investigate the importance of KCa channels to α-cell electrical excitability, calcium handling, and GCG secretion. α-cells display a KCa current, which is partially inhibited by blocking small conductance KCa (SK) or big conductance KCa (BK) channels. Inhibition of P/Q-type VDCCs, sarco/endoplasmic reticulum (ER) calcium-ATPases (SERCA), and KCa channels also partially inhibit this current. It is likely that calcium influx through VDCCs triggers calcium-induced calcium release (CICR) from ER calcium stores activating α-cell KCa channels. The inhibition of SK channels transiently increases calcium influx into α-cells at 1 mM glucose, however, over time intracellular calcium decreases. This may be due to voltage-dependent inactivation of α-cell VDCCs. Interestingly, SK channel inhibition reduces GCG secretion at 1 mM glucose while SST secretion is unaffected. Thus, it is likely that this is an intrinsic α-cell effect. These findings demonstrate that α-cells possess a KCa current and that its activation is important for α-cell electrical activity, Ca2+ handling, and GCG secretion.

Supported By: American Diabetes Association (1-17-IBS-024 to D.J.), National Institutes of Health (DK097392, DK097392, Vanderbilt University (P60DK20593, T2D010103)

Supported By: University of Southern California

STIM1/Orai1 Inhibition Reduces Store-Operated Ca2+ Entry and Modulates α-Cell Glucagon Secretion

MOLLY K. ALTMAN, PRASANNA DADI, DAVID JACOBSON, Nashville, TN

In type 2 diabetic patients glucagon secretion becomes dysregulated under elevated glucose conditions worsening hyperglycemia. However, the mechanisms of glucose inhibition of glucagon secretion remain incompletely understood. Therefore, we sought to uncover the glucose dependent mechanisms that modulate pancreatic α-cell glucagon secretion. One mechanism that regulates α-cell Ca2+ influx in a glucose dependent manner is store-operated Ca2+ entry (SOCE). Therefore, in our studies we used a small molecule (AnCoA) that inhibits the STIM1/Orai1 protein interaction and prevents store-operated Ca2+ channel activation. In whole mouse islet α-cells inhibition of SOCE with AnCoA reduced Ca2+ influx in 1 mM glucose (8.4% ± 1.1%). We went on to test the influence of SOCE on glucose modulation of glucagon secretion, in 1 mM glucose AnCoA reduced glucagon secretion in mouse pancreatic islets (53.5% ± 11%). However, there was no significant change in glucose inhibition of glucagon secretion by inhibition of SOCE at 11 mM glucose. To follow-up on this, we used transgenic mice without STIM1 in α-cells and showed that AnCoA does not influence Ca2+ fluctuations in knockout islet α-cells. This proves in our hands that AnCoA works selectively. Additionally, we used transgenic GCAMP3 mice without STIM1 in α-cells for whole islet confocal studies to measure SOCE in 1 mM and 11 mM glucose conditions. We found that in whole islet α-cells without functional STIM1, Ca2+ influx due to SOCE was reduced in 1 mM glucose. Next, we wanted to test this molecule in human islet calcium homeostasis studies. Human dispersed α-cells show inhibition of SOCE with AnCoA treatment in 1 mM glucose conditions Thus, our findings identify that inhibition of STIM1/Orai1 reduces SOCE in low glucose conditions leading to decreased α-cell glucagon secretion.

Supported By: National Institutes of Health (DK098166, DK097392), Vanderbilt University (P60DK20593 to D.J.)