2566-PUB

Identification of New GWAS Markers for Gene-Environment Interaction in Metabolic Syndrome and Its Components in Mediterranean Populations

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Metabolic syndrome (MetS) is a complex condition involving susceptibility genes recently identified by GWAS. To understand the role of gene-environment (GxE) interaction and ameliorate GWAS we investigated high density SNP (Single Nucleotide Polymorphism) in MetS from MEDIGENE collections composed of French, Romanians, Spanish, Greeks, Turkish and Italians (n = 916). Selected genes were tested by leader SNPs and at 1000 Genome Project density by customized MEDISCOPE chip (Affymetrix) with 758,000 SNPs. We selected 190 genes from CardioGxE catalog involved in regulation of energy consumption (30), fat, protein and carbohydrate intake (80), poly-, mono-unsaturated and saturated fatty acids (80) and genes for Mediterranean diet (91). Only 16 genes were common with previous GWAS for MetS. With leader SNPs the association was weak, except strong signals correlated with low level of HDL for TCF7L2 ($P = 6.11 \times 10^{-7}$) and CEPT ($P = 2.0 \times 10^{-4}$). Two genes of lactase persistence were equally correlated with low HDL levels. High density genotyping (3924 SNP) confirmed the role of FTO, IRX3, C2orf43, GCK, LIPC, ADIPOQ, LPL, TCF7L2, APOA1 and LEPR on MetS and HDL levels (sustained by Bonferroni correction). Among 42 leader SNPs of Mediterranean diet interaction, MetS was associated with rs5128 of APOC3 (OR 1.53 CI% [1.14-2.06], P = 0.003) while at high density (5148 SNP) the most influential SNPs were recognized for FTO, IRS1, LPL and APOA5 cluster. These data indicate that among GxE registered SNPs, stronger markers with clinical significance may be obtained for MetS as well as for modifier genomic regions. Involvement of lactase persistence gene suggests potential use in stratification of geographically disperse populations around Mediterranean area. We concluded that GWAS for MetS in Europeans should be entirely revised by increasing SNP density and considering geographical, ancestry and admixture data with Eastern and North African populations.

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IMMUNOLOGY

2567-PUB

Role of Hybrid Insulin Peptides in the Development of Type 1 Diabetes

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We recently discovered a new class of autoantigens that is targeted by diabetes triggering T cells in nonobese diabetic mice, as well as T cells isolated from the residual islets of type 1 diabetic (T1D) organ donors. These antigens form through the covalent cross-linking of insulin fragments to other peptide cleavage products found in the granules of beta cells. The resulting hybrid insulin peptides (HIP) contain novel amino acid motifs that are recognized as foreign by disease driving T cells, leading the T cells to mediate the destruction of beta cells. In this study, we test if T cells, isolated from the residual islets of T1D donors, respond to synthetic HIPs from a large panel of distinct peptides. The identification of antigens, that are recognized by pathogenic T cells, may provide us with tools necessary to re-educate the immune system of T1D patients or predisposed individuals to become tolerant towards insulin producing beta cells.

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2568-PUB

Higher Negative Rate of AFP and Lower AFP Level Were Found in Patients with Primary Hepatic Carcinoma and Diabetes

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It has been found that the risk of hepatic carcinoma in diabetic patients was significantly elevated. As an important tumor marker of hepatic carcinoma, does AFP have special features in diabetic patients? To explore it, 304 patients previously diagnosed with primary hepatic carcinoma were selected and divided into diabetic group (n=138) and nondiabetic group (n=166). Liver function was assessed by Child-Pugh classification by Barcelona Clinic Liver Cancer, and pathology classification by Edmondso n-Steiner. Comparison of AFP and other tumor markers, correlation of FPG, HbA1c with AFP, and characteristics of AFP in different cancer stages, levels and liver function in both groups were analyzed. Compared to nondiabetic group, diabetic patients had higher negative rate of AFP (56.52% vs. 37.95%), lower levels of AFP (Ln transformation: 3.06±2.49 vs. 4.22± 2.63 ug/L, p<0.001), and worse liver function (μ=-2.21, p=0.02 8). In diabetic group, significant growing tendency of AFP associated with reducing liver function (Ln transformation: 4.05 ±2.57 vs. 2.78±2.41 vs. 0.14±0.66, p=0.025) was found. Meanwhile, AFP negatively correlated with liver function (r=-0.287, p=0.016) and prothrombin time (PT) (r=-0.388, p=0.001). Also, AFP differed significantly among cancer stages (Ln transformation: 2.74 ±2.27 vs. 5.99±1.09 vs. 3.09±2.51 vs. 2.36±2.3, p=0.048). There was a growing tendency of AFP along with elevating pathology grades (p>0.05). No significant correlation was found between FPG, HbA1c and AFP. In addition, CEA, CA153, CA125, CA199, CA242 an dCY FRA211 of diabetic group were significantly higher (p<0.05). Previously diagnosed primary hepatic carcinoma patients with diabetes had higher negative rate of AFP, lower levels of AFP and worse liver function. Thus, low AFP in diabetic patients may delay early diagnosis of primary hepatic carcinoma. Abnormal liver function and slight elevation of AFP found in diabetic patients raise suspicion of hepatic carcinoma.

2569-PUB

Acromegaly Presenting as Severe Uncontrolled Diabetes

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We report a case of newly diagnosed acromegaly in a patient with diabetes and highly positive autoimmune antibodies.

A 31 year-old female presented to the emergency room with severe frontal headaches. Her past medical history was significant for type 2 diabetes mellitus for two years, treated with metformin and glyburide. She was hyperglycemic with glucose of 393 mg/dL and A1c of 12.2%. Fasting insulin was 16.0 uU/mL, fasting glucose of 314 mg/dL and c-peptide of 2.3 ng/mL (0.9-4.3). Further work-up showed an elevated IGF-1 of 728 (113-297 ng/mL), and random GH of 33.4 (0.05-8.0 ng/mL). MRI of the brain showed a sellar mass measuring 1.9 x 1.5 x 1.1 cm. During hospitalization insulin was started with dose increased progressively to an average of 100 units a day (1.2 unit/kg). Transphenoidal mass resection confirmed the diagnosis with tumor strongly staining for GH. Insulin requirements appreciably declined after surgery to 20 units daily (0.2 unit/kg). Laboratory workup 12 weeks after surgery showed persistent rise of GH to 1.8 ng/mL and IGF-1 of 320 ng/mL with fasting insulin of 10.06 uU/mL, glucose 184 mg/dL and c-peptide of 1.9 ng/mL. A 75 gm OGTT showed nadir GH of 1.42ng/mL indicating residual disease. On further examination, patient was found to have highly positive anti-GAD 65 of 1,200 (<6IU/mL), and zinc T8 transporter of >5,000 (0-15 u/mL).

Discussion: Twenty percent of treatment-naïve acromegaly patients have diabetes at diagnosis. GH antagonizes insulin action, increases lipolysis and reduction of GH levels is expected to ameliorate glucose homeostasis. Even though it was initially thought that our patient had hyperglycemia solely secondary to acromegaly, the presence of two high titer antibodies is nearly 100% specific for diagnosis of type 1 diabetes mellitus.

In conclusion, this case poses a challenging diagnosis in the setting of several mechanism of hyperglycemia superimposed concomitantly, presenting as a mixture of insulin resistance from acromegaly and obesity, on background of beta cell failure from autoimmunity.

TRANSPLANTATION

2570-PUB

Fasting Hypoglycemia in a Child after Total Pancreatectomy with Islet Autotransplantation

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Introduction: Total pancreatectomy with islet autotransplantation (TPIAT) is a treatment option for selected children with chronic pancreatitis who suffer from debilitating pain and impaired quality of life. Fasting hypoglycemia is a complication recently reported in adults following TPIAT, but until now it has not been described in children. We review a case of insulin-independent fasting hypoglycemia in an adolescent female, occurring 10 months after TPIAT.

Case: A 12-year-old female with SPINK1 and CFTR mutations and pancreas divisum underwent TPIAT for chronic pancreatitis. Ten months post-TPIAT, she developed recurrent hypoglycemia as low as 45 mg/dL on a total daily insulin dose of only 0.03 units/kg, prompting complete discontinuation of insulin therapy. Approximately 20 hours after her last rapid-acting insulin exposure, she had an episode of fasting hypoglycemia (glucose measurement of 33 mg/dL on home glucometer). Her continuous glucose monitor (CGM) report documented two separate, precipitous drops in glucose overnight. Adrenal insufficiency and fatty acid oxidation disorders were ruled out. She was instructed to take frequent, small meals and avoid high

For author disclosure information, see page A751.

glycemic index carbohydrates. Over two months, low dose basal and bolus insulins were restarted due to intermittent hyperglycemia. On this insulin regimen and revised diet, there have been no further episodes of severe fasting hypoglycemia.

Conclusion: This is the first report of fasting hypoglycemia occurring after TPIAT in a pediatric patient. In addition, the use of CGM allowed for documentation of glucose trends and notification of the event with an alarm. Although the pathophysiology is incompletely understood, dysregulation of glucagon secretion in the transplanted islet cells has been hypothesized in other reports. Based upon the clinical course described, fasting hypoglycemia in patients post-TPIAT is a potential complication that should be recognized and safeguarded against in children as well as adults.

2571-PUB

A Pilot Trial to Investigate Efficacy and Safety of an Automatized Decision Support System for the Treatment of Steroid-Induced Hyperglycemia in Patients with Acute Graft-vs.-Host-Disease

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Graft-versus-host-disease (GvHD) is a common and life-threatening complication in patients undergoing allogeneic stem cell transplantation. Since high-dose systemic glucocorticoids are the established first-line therapy, about half of these patients develop steroid-induced hyperglycemia, which has been associated with adverse outcome in this patient population. Adequate glucose control in these patients proved to be challenging. We aimed to investigate whether glucose control with an automatized decision support system is effective and safe in this patient group.

We randomly assigned 10 patients with acute GvHD and hyperglycemia (2 independent fasting glucose values >140mg/dL) while receiving corticosteroid therapy to either an automated decision support system (GlucoTab®, GT) or conventional treatment (CON) according to local standards. Glycemic control was assessed by frequent glucose measurements during hospital stay. Follow-up period was 6 months.

The percentage of glucose values within the target range (70-180 mg/dL) was 67.2% for GT vs. 65.4% for CON. The percentage of hypoglycemic values was lower for GT (0.8% vs. 2.3%) while hyperglycemia rates were comparable (32.0% vs. 32.2%). Maximum total daily insulin dose was 73 for GT and 28.4 U for CON, respectively.

Insulin treatment guided by a decision support system was effective and safe in subjects with steroid induced hyperglycemia during hospital stay. Further optimization of the algorithm for high-dose steroid treatment is required to reduce hyperglycemia rates. To verify that good glycemic control improves outcome larger studies are needed in this patient population.

INSULIN ACTION—ADIPOCYTE BIOLOGY

2572-PUB

The Effect of AMPK Activation on Inflammatory Cytokine in Mature Hypertrophied 3T3-L1 Adipocyte

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High fat and high calorie intake as well as the decline of physical activity leads to obesity, insulin resistance and more over metabolic syndrome, concomitant with increased visceral fat mass which is mainly caused by hypertrophy of adipocyte. Recently we have reported that by activating endogenous AMPK using 2, 4-dinitrophenol, release of monocyte chemoattractant protein-1(MCP-1) (a key inflammatory cytokine in insulin resistance) significantly decreases in mature 3T3-L1 adipocytes (BBRC 419:200-205, 2012). However the molecular mechanism underlying this pathway is not completely understood. To elucidate the role of AMPK, in this study, we observed the effect of AMPK activation toward MCP-1 release and deposit of triglyceride in vitro model of artificially hypertrophied mature 3T3-L 1 adipocytes preloaded with palmitate. 3T3-L1 adipocytes were cultured with 300mmol/L palmitate for 24 h with or without pretreatment of AMPK activator [0.5mM AICAR (5-Aminomidazole-4-carboxamide ribonucleotide), 1mM AICAR, 25μM A-769662 or 2.5mM metformin]. Intracellular MCP-1 mRNA, protein, secretion of MCP-1, triglyceride contents and phosphorylated NFκB p65, ACC (Acetyl-CoA carboxylase) were quantified respectively. The cell showed hypertrophy by high palmitate with marked elevation of triglyceride, intracellular MCP-1 mRNA, protein, secretion of MCP-1 and phosphorylated NFκB. On the other hand, pretreatment of AMPK activators increased the phosphorylation of ACC, and then inhibited the palmitate induced elevation of not only the intracellular MCP-1 but also the phosphorylated NFκB. Interestingly, metformin showed the same effect as other AMPK activators.

In summary, our result demonstrated that activation of AMPK signaling decreases MCP-1 expression and the deposit of triglyceride in hypertrophied mature 3T3-L1 adipocytes. Increases in phosphorylated NFκB and ACC were considered to be, at least one part of the underlying molecular mechanisms.

2573-PUB

Total Adiponectin and Adiponectin Multimeric Complexes Show Variable Associations with Metabolic Indices and Glycemic Status

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Introduction: Adiponectin, a protective adipokine that increases insulin sensitivity (IS) and regulates glucose metabolism circulates in plasma as high (HMW), medium (MMW) and low molecular weight forms (LMW). Studies show the HMW form as the best indicator of IS. This study compares Total Adiponectin (TA) and the multimeric complexes according to their associations with metabolic and glycemic status.

Methods: Fasting TA, HMW, MMW, LMW, insulin, glucose, lipid profile and HbA1c were measured in 109 patients with type 2 diabetes (T2DM) and 112 nondiabetic first degree relatives. Clinical and anthropometric data were recorded. Subjects were classified by adiposity, insulin resistance (IR homeostasis model assessment) and the number of criteria of Metabolic Syndrome (MetS) (IDF criteria).

Results: TA (r = -0.21 and -0.24), HMW (r = -0.37 and -0.38) were significantly ($p<0.05$) inversely correlated with BMI and waist circumference respectively but MMW and LMW were not. TA (r = 0.23 and -0.24), HMW (r = 0.40 and -0.39) were significantly correlated with IS and IR respectively but MMW and LMW were not. Compared to HMW, Receiver Operating Characteristic (ROC) analysis showed that TA had the higher area under the curve for diagnoses of MetS (0.749 vs. 0.712) and T2DM (0.644 vs. 0.612) whereas HMW had the higher area under the ROC curve for diagnosis of IR (0.629 vs. 0.689).

Conclusions: Circulating TA and multimeric complexes show variable associations with metabolic indices and glycemic status. Our results suggest that MMW and LMW forms of adiponectin are not a major determinants of the metabolic perturbations of the adipokine. HMW is a better predictor of IR but TA is a better predictor of T2DM and MetS. As multimerisation is genetically determined, the predominant form of adiponectin could be the main determinant of the metabolic phenotype and disease associations. Multimeric forms should always be considered in the interpretation of the associations of circulating adiponectin.

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2574-PUB

Adipocytokines and Cardiometabolic Risk in a Biracial Cohort

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Adipocytokines are associated with diabetes risk, but their link with cardiometabolic risk in diverse populations is unclear. We evaluated circulating adipocytokines in relation to adiposity, lipids, and glucoregulation in African Americans (AA) and European Americans (EA).

We studied 376 normoglycemic subjects (217 AA, 159 EA), all offspring of parents with type 2 diabetes. Each subject had clinical exam, OGTT, and lab tests including adipocytokines (hsCRP, TNF-α, IL-6, IL-1, resistin, and adiponectin). We also assessed insulin sensitivity (Si-clamp), beta-cell function, and body composition by dexa. Total Pro-inflammatory Cytokine Score (PCS) was derived as (hsCRP + TNF-α + IL-6 + IL-1 + resistin).

The mean (± SD) age of the subjects was 44.2 ± 10.6 yr; BMI 30.2 ± 7.2kg/m2, fasting plasma glucose (FPG) 91.8 ± 6.8mg/dl and 2hr PG was 121.8 ± 24.4mg/dl. Adiponectin was lower (8.34 ± 4.95 μg/ml vs. 10.7 ± 5.44 μg/ml, $P<0.0001$), and hsCRP (4.67 ± 6.62 mg/L vs. 2.77 ± 4.55 mg/L, $P=0.003$) and PCS (25.4 ± 12.3 vs. 22.51 ± 9.1, $P=0.02$) higher in AA vs. EA. Significant associations were seen between cardiometabolic measures (BMI, waist circumference, total and trunk fat, FPG, 2hrPG, HDL, triglycerides) and individual adipocytokines ($P= 0.04 - < 0.0001$), the strongest being with BMI ($r=0.55$ in AA, $r=0.60$ in EA, $P< 0.0001$). Individual and total pro-inflammatory cytokines were associated with insulin resistance, whereas adiponectin predicted greater insulin sensitivity ($P=0.04 - <0.0001$). Weaker and less consistent associations were noted between various adipocytokines and insulin secretion, the strongest being with adiponectin ($r= -0.21$, $P=0.0002$).

In conclusion, circulating adipocytokines display congruent relationships with adiposity, lipids, insulin sensitivity, and insulin secretion among normo-