Altersations in Postprandial Hepatic Glycogen Metabolism in Type 2 Diabetes

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Decreased skeletal muscle glucose disposal and increased endogenous glucose production (EGP) contribute to postprandial hyperglycemia in type 2 diabetes, but the contribution of hepatic glycogen metabolism remains uncertain. Hepatic glycogen metabolism and EGP were monitored in type 2 diabetic patients and nondiabetic volunteer control subjects (CON) after mixed meal ingestion and during hyperglycemic-hyperinsulinemic-somatostatin clamps applying 13C nuclear magnetic resonance spectroscopy (NMRS) and variable infusion dual-tracer technique. Hepatocellular lipid (HCL) content was quantified by 1H NMRS. Before dinner, hepatic glycogen was lower in type 2 diabetic patients (227 ± 6 vs. CON: 275 ± 10 mmol/l liver, P < 0.001). After meal ingestion, net synthetic rates were 0.76 ± 0.16 (type 2 diabetic patients) and 1.36 ± 0.15 mg · kg−1 · min−1 (CON, P < 0.02), resulting in peak concentrations of 283 ± 15 and 360 ± 11 mmol/l liver. Postprandial rates of EGP were −0.3 mg · kg−1 · min−1 (30–170 min; P < 0.05 vs. CON) higher in type 2 diabetic patients. Under clamp conditions, type 2 diabetic patients featured −54% lower (P < 0.03) net hepatic glycogen synthesis and −0.5 mg · kg−1 · min−1 higher (P < 0.02) EGP. Hepatic glucose storage negatively correlated with HCL content (R = −0.602, P < 0.05). Type 2 diabetic patients exhibit 1) reduction of postprandial hepatic glycogen synthesis, 2) temporarily impaired suppression of EGP, and 3) no normalization of these defects by controlled hyperglycemic hyperinsulinemia. Thus, impaired insulin sensitivity and/or chronic glucolipotoxicity in addition to the effects of an altered insulin-to-glucagon ratio or increased free fatty acids accounts for defective hepatic glycogen metabolism in type 2 diabetic patients. Diabetes 53:3048–3056, 2004

Under normal life conditions, meals are ingested every few hours, therefore rendering humans in the postprandial state for approximately half of the day. Knowledge of glucose metabolism after meal ingestion is central to the understanding of the pathophysiology and characterization of potential therapeutic targets in the diabetic state. Many previous studies in type 2 diabetic patients demonstrated defects in skeletal muscle glucose metabolism during experimental hyperinsulinemic hyperglycemia (1,2) and recently also after meal ingestion (3).

Nevertheless, the liver is almost exclusively responsible for endogenous glucose production (EGP), which correlates with the degree of hyperglycemia after an overnight fast (4–8) and is less suppressed in type 2 diabetic patients after meal ingestion (6,9–13). Invasive hepatic vein catheter studies suggested that splanchnic glucose uptake is decreased in type 2 diabetic patients (14,15). Impaired insulin-stimulated hepatic glucose uptake was confirmed in type 2 diabetic patients by positron emission tomography (16). Using a needle biopsy technique, Beringer and Thaler (17) demonstrated decreased hepatic glycogen concentrations in elderly diabetic patients. Noninvasive 13C nuclear magnetic resonance spectroscopy (NMRS) studies found lower hepatic glycogen breakdown and increased gluconeogenesis in type 2 diabetic patients (18,19), but the contribution of liver glycogen metabolism to postprandial hyperglycemia and its sensitivity to insulin in type 2 diabetic patients remains uncertain.

Under steady-state conditions (clamp technique), the portal vein insulin, glucagon, and free fatty acid (FFA) concentrations regulate hepatic glucose metabolism in nondiabetic humans (20–25). Furthermore, increased liver fat accumulation (hepatocellular lipid [HCL] content) was found to correlate negatively with peripheral insulin sensitivity and insulin-dependent suppression of EGP (7,26). However, the impact of these factors on hepatic glycogen metabolism in type 2 diabetic patients is uncertain.

Thus, this study examined hepatic glycogen metabolism in type 2 diabetic patients and matched nondiabetic volunteers 1) after mixed meal ingestion and 2) during hyperglycemic-hyperinsulinemic-somatostatin clamps. We used noninvasive 13C NMRS (18,27,28) to directly quantify net postprandial hepatic glycogen synthesis (protocol A) and variable infusion dual-tracer technique (6,27,29) to assess the postprandial time course of EGP (protocol B).

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Received for publication 23 June 2004 and accepted in revised form 1 September 2004.

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EGP, endogenous glucose production; FFA, free fatty acid; HCL, hepatocellular lipid; NMRS, nuclear magnetic resonance spectroscopy. © 2004 by the American Diabetes Association.
For evaluation of the role of hepatic insulin sensitivity in type 2 diabetic patients, we also measured flux through hepatic glycogen synthase, simultaneous flux through hepatic glycogen phosphorylase, and EGP under conditions of matched hyperglycemia, hyperinsulinemia, hypoglycagomina, and decreased plasma FFA concentrations (clamp test, protocol C).

**RESEARCH DESIGN AND METHODS**

We studied seven type 2 diabetic patients (five men/two women, age 56 ± 3 years, BMI 26.9 ± 0.6 kg/m², known diabetes duration 7 ± 2 years, HbA1c 7.1 ± 0.3%, triglycerides 254 ± 49 mg/dl) and seven glucose-tolerant humans (five men/two women, age 49 ± 2 years, BMI 25.8 ± 0.9 kg/m², HbA1c 5.2 ± 0.1%, triglycerides 130 ± 32 mg/dl) during mixed-meal protocols (protocols A and B). Subsequently, we studied six type 2 diabetic patients (five men/one woman, age 53 ± 4 years, BMI 26.1 ± 0.7 kg/m², known diabetes duration 6 ± 2 years, HbA1c 7.4 ± 0.1%, triglycerides 221 ± 15 mg/dl) and six healthy humans (four men/two women, age 55 ± 4 years, BMI 27.5 ± 0.7 kg/m², HbA1c 5.4 ± 0.1%, triglycerides 102 ± 17 mg/dl) during hyperglycemic-hyperinsulinemic clamp tests (protocol C). Four type 2 diabetic patients and four nondiabetic volunteer control subjects (CON) participated in all three protocols. Type 2 diabetic patients had no history of insulin or thiazolidinediones therapy and stopped their hypoglycemic agents for at least 3 days before each protocol. Female participants were either postmenopausal or were studied in the first half of their menstrual cycle. All volunteers were on an isocaloric diet and refrained from physical exercise for at least 3 days before each protocol. Samples were drawn for measurement of plasma glucose and insulin, HbA1c, triglycerides, and total cholesterol.

**Protocol A.** Hepatic glycogen concentrations were measured using 13C NMRs (28,30) before (4:00–4:30 p.m.) and after dinner (6:00–7:00 p.m., 8:00–9:00 p.m.) in CON and 6:00–10:30 p.m. in type 2 diabetic patients. Nondiabetic volunteers were admitted at 6:00 a.m. the day of the study.

**Protocol B.** At 3:00 p.m., a primed (20 μmol/kg per 5 mmol/l) continuous (0.020 μmol · kg⁻¹ · min⁻¹) infusion of [6,6-2H₂]glucose (99% enriched) was started for measurement of EGP (28). At 9:00 a.m. (0 min), a hyperglycemic-hyperinsulinemic-pancreatic clamp test was initiated by somatostatin (−5 to 300 min; 0.1 μg · kg⁻¹ · min⁻¹; UCB Pharma, Vienna, Austria) (28). Nondiabetic volunteers were admitted at 6:00 a.m. the day of the study.

**Protocol C.** Type 2 diabetic patients were admitted the evening before the study, and plasma glucose concentrations were normalized overnight using intravenous insulin infusion (Actrapid; Novo Nordisk, Vienna, Austria) (28). Nondiabetic volunteers were admitted at 6:00 a.m. the day of the study.

At 6:30 a.m. (~150 min), a primed-continuous infusion of [6,6-2H₂]glucose was started for measurement of EGP (28). At 9:00 a.m. (0 min), a hyperglycemic-hyperinsulinemic-pancreatic clamp test was initiated by somatostatin (~5 to 300 min; 0.1 μg · kg⁻¹ · min⁻¹; UCB Pharma, Vienna, Austria) and insulin (0–5 min: 80 mU · m⁻² · min⁻¹; 5–20 min: 40 mU · m⁻² · min⁻¹; 20–100 min: 10 mU · m⁻² · body surface area; Actrapid) infusion. Plasma glucose was raised and maintained at ~180 mg/dl by primed (0.2 g/kg) variable dextrose infusion (20% wt/vol) enriched with [1-13C]glucose (20% wt/wt) and [6,6-2H₂]glucose (2% wt/wt). For assessment of the flux through hepatic glycogen phosphorylase, the [1-13C]glucose-labeled infusion was switched to natural abundance [1-13C]glucose infusion at 150 min (21–23). Hepatic glycogen concentrations were measured before the clamps (~30 to 0 min), from 60 to 150 min and from 210 to 300 min during the clamps with 13C NMRs, as previously published (28,30). Contributions of the direct and gluconeogenic pathways to glycogen synthesis were assessed with 1,000 mg acetoacetinophen given orally at ~30 min (27,28,31). HCL content was measured before the clamp test. During the clamps, plasma samples for measurement of 13C enrichments in glucose and gluconolactone and 1H enrichments in glucose were drawn at 15-min intervals.

**Liver 13C and 1H NMRs.** Localized 13C NMR spectra were obtained in the 37/80 cm Medspec (Bruker Biospin, Ettlingen, Germany) with a 10-cm circular 13C/1H transmitter/receiver coil placed over the lateral aspect of the liver, applying a modified one-dimensional inversion-based sequence (28,30). Absolute glycogen concentrations were obtained by comparing the C1 glycogen peak (100.5 ppm) integral of liver spectra with that of a glycogen standard taken under identical conditions. To eliminate the contribution of [1-13C]glucose to the [1-13C]glycogen spectral line intensity during labeled glucose infusion in protocol C, only the left half of the [1-13C]glycogen doublet in the spectra was integrated. Corrections for loading of the coil and sensitive volume of the coil were performed.

Localized 1H NMR spectra of the liver were acquired using the same magnetic resonance system, coil, and patient placement inside the magnet applying the breath-hold–triggered stimulated echo acquisition mode sequence (7). HCL content was quantified by integration of the CH₂ and CH₃ group resonances and is expressed in arbitrary units (AU) as a percentage of total 1H NMR signals (water + lipid).

**Analytical procedures.** Plasma glucose was measured by the glucose oxidase method (Glucose Analyzer II; Beckman Instruments, Fullerton, CA). Plasma FFAs were assayed microfluorimetrically (Wako Chemicals, Richmond, VA). Plasma immunoreactive insulin, C-peptide, and glucagon were measured by commercially available radioimmunoassays (24,32,33). Atom percent excess of 1H and 13C in plasma glucose and 13C atom percent excess in plasma acetoacetinophen glucuronide were quantified with gas and liquid chromatography–mass spectroscopy, respectively (28).

**Calculations**

**Hepatic glycogen metabolism.** Rates of net hepatic glycogen synthesis and subsequent net glycogenolysis during protocol A were calculated from linear regression of the individual glycogen concentration time curves over respective time periods of increasing (6:00 to ~9:00 p.m. in CON and 6:00 to 10:30 p.m. in type 2 diabetic patients) and decreasing (10:00 p.m. to 6:00 a.m.) glycogen concentrations (28,30). The time point of the peak glycogen concentration
Hepatic glycogen concentrations were lower in type 2 diabetic patients before dinner (type 2 diabetic patients: 227 ± 6 vs. CON: 275 ± 10 mmol/l, P < 0.001, Fig. 3A) and remained unchanged for 1 h after dinner (type 2 diabetic patients: 227 ± 10 vs. CON: 265 ± 11 mmol/l, P < 0.001). Liver glycogen increased afterward to mean individual peak values of 283 ± 15 mmol/l in type 2 diabetic patients and 360 ± 11 mmol/l in CON (P < 0.01), with a time lag of −55 min between the groups (calculated peak time; type 2 diabetic patients: 302 ± 15 min vs. CON: 247 ± 17 min; P < 0.05). The difference between lowest individual preprandial and highest individual postprandial glycogen concentration was 86 ± 7 mmol/l in CON and 56 ± 12 mmol/l in type 2 diabetic patients (P < 0.05). Rates of net glycogen synthesis (Fig. 4A) were −44% lower in type 2 diabetic patients (0.76 ± 0.16 vs. CON: 1.36 ± 0.15 mg·kg⁻¹·min⁻¹, P < 0.05). The direct pathway contributed similarly to glycogen synthesis in both study groups (type 2 diabetic patients: 60 ± 4% vs. CON: 56 ± 2%, P = 0.514). Overnight, hepatic glycogen concentrations decreased linearly, reaching values of −215 mmol/l in both groups in the morning (Fig. 3A). Rates of net glycogenolysis were −50% lower in type 2 diabetic patients (0.37 ± 0.08 vs. CON: 0.75 ± 0.09 mg·kg⁻¹·min⁻¹, P < 0.01) (Fig. 4A).

Before dinner, EGP was −13% higher in type 2 diabetic patients (1.95 ± 0.07 vs. CON: 1.73 ± 0.07 mg·kg⁻¹·min⁻¹, P < 0.05) (Fig. 4B). After dinner, EGP decreased in both groups but remained −0.3 mg·kg⁻¹·min⁻¹ higher in type 2 diabetic patients from 30–170 min (0.98 ± 0.11 vs. CON: 0.68 ± 0.05 mg·kg⁻¹·min⁻¹, P < 0.05). Time course of EGP reached the nadir in CON at 60–90 min, but only at 240 min in type 2 diabetic patients, i.e., the maximum suppression of EGP occurred delayed in type 2 diabetic patients. Thereafter, EGP was similar in both groups and returned to −60–70% of predinner values at 480 min. Rates of postabsorptive gluconeogenesis in the time period of 11:00 p.m. to 1:00 a.m. represented 67 ± 8% of EGP in type 2 diabetic patients but only 43 ± 4% (P < 0.05) of EGP in CON.

Clamp tests. During the hyperglycemic-hyperinsulinemic clamp tests, plasma glucose, FFAs, insulin, and glucagon were not different between both groups (Fig. 2E–H). Whole-body glucose uptake was −37% lower in type 2 diabetic patients (180–300 min: type 2 diabetic patients: 8.03 ± 0.35 mg·kg⁻¹·min⁻¹ vs. CON: 12.73 ± 0.48 mg·kg⁻¹·min⁻¹, P < 0.05).

Before the clamp test, both study groups exhibited similar hepatic glycogen concentrations (type 2 diabetic patients: 218 ± 10 vs. CON: 234 ± 9 mmol/l, P = 0.28, Fig. 3B). During the clamp, hepatic glycogen concentrations increased linearly in both groups (Fig. 3B), but V_{syn} was −46% lower in type 2 diabetic patients (0.63 ± 0.12 vs. CON: 1.17 ± 0.15 mg·kg⁻¹·min⁻¹, P < 0.05), with similar contribution of the direct pathway in both groups (type 2 diabetic patients: 60 ± 10% vs. CON: 65 ± 2%, P = 0.416). Simultaneous V_{out} (Fig. 5A) was not different (type 2 diabetic patients: 0.21 ± 0.07 vs. CON: 0.23 ± 0.11 mg·kg⁻¹·min⁻¹, P = 0.805), resulting in −54% lower rates of net hepatic glycogen synthesis (Fig. 5A) in type 2 diabetic patients (0.42 ± 0.10 vs. CON: 0.91 ± 0.16 mg·kg⁻¹·min⁻¹, P < 0.05). Relative hepatic glycogen turnover was
FIG. 2. Plasma concentrations of glucose, FFAs, and major glucoregulatory hormones in type 2 diabetic patients (○) and CON (▲) after ingestion of a mixed-meal dinner (arrow) (A–D) and during hyperglycemic-hyperinsulinemic-somatostatin clamp tests (E–H). *P < 0.05 for type 2 diabetic patients vs. CON.
slightly but not significantly increased in type 2 diabetic
patients (31 ± 11% vs. CON; 19 ± 11%, P = 0.460).

EGP was ~30% higher in type 2 diabetic patients before
the clamp (type 2 diabetic patients: 2.38 ± 0.10 vs. CON:
1.83 ± 0.05 mg · kg⁻¹ · min⁻¹, P < 0.01) and remained so
during the clamp (120–300 min: type 2 diabetic patients:
0.53 ± 0.05 vs. CON: 0.04 ± 0.04 mg · kg⁻¹ · min⁻¹, P <
0.02) (Fig. 5B).

Hepatocellular lipid content was three times higher in
type 2 diabetic patients (9.9 ± 2.5 AU vs. CON: 2.8 ± 0.7
AU, P < 0.05) and negatively correlated across the whole
study population with rates of net hepatic glycogen syn-
thesis (R = −0.602, P < 0.05) as well as with rates of
whole-body glucose uptake (R = −0.576, P < 0.05) during
the clamp test.

DISCUSSION
This study provides the time course of cumulative glyco-
gen storage and rates of net hepatic glycogen synthesis in
type 2 diabetic patients under physiological conditions of
mixed-meal ingestion as well as under that of experimen-
tal stimulation of glycogen accumulation. Postprandial
glycogen synthesis is reduced in mildly overweight type 2
diabetic patients and is accompanied by a temporarily
impaired EGP suppression. Because these defects of post-
prandial hepatic glucose metabolism of type 2 diabetic
patients were observed during decreased insulin-to-gluca-
gon ratios and impaired FFA suppression, we also as-
sessed hepatic glucose metabolism under conditions of
hyperinsulinemic hyperglycemia combined with low glu-
cagon and FFA concentrations. Under these conditions,
glycogen synthesis and suppression of EGP remained
clearly impaired in type 2 diabetic patients.

Postprandial conditions. After dinner, glycogen accu-
mulation rose by ~86 mmol/l above preprandial concen-
tration in CON in ~4.5 h, accounting for storage of ~26 g
carbohydrates in the liver, which is similar to previous
findings in nondiabetic humans (27). In type 2 diabetic
patients, glycogen concentrations rose only by 56 mmol/l
liver within ~5.5 h after meal ingestion, resulting in
storage of ~17 g carbohydrates in the liver. Thus, type 2
diabetic patients exhibit reduction of net hepatic glycogen

![Mixed Meal Test](image1)

![ Clamp Test](image2)

FIG. 3. Time course hepatic glycogen concentration during a
mixed-meal test (A) (protocol A, −120 to 960 min) and during
the pulse period of the clamp test (B) (protocol C, −30 to 150
min) in type 2 diabetic patients (○) and CON (▲). A: *P < 0.05,
type 2 diabetic patients vs. CON; §P < 0.05 vs. basal in CON;
§§P < 0.05 vs. basal in type 2 diabetic patients. B: Mean Pearson
coefficient for linear regression of measured hepatic glycogen
concentrations versus time was R = 0.96 ± 0.01 in CON and R =
0.77 ± 0.12 in type 2 diabetic patients.
accumulation by −35%, suggesting that decreased hepatic glycogen storage contributes to their postprandial hyperglycemia.

A similar defect was observed in glucokinase-deficient maturity-onset diabetes of the young (MODY)-2 patients (38), in whom the impaired hepatic glucokinase activity is held responsible for the reduction in the contribution of glucose (the direct pathway) to hepatic glycogen synthesis (38). Of note, in the present study, the relative contribution of the direct pathway was unchanged in type 2 diabetic patients after the meal as well as during the clamp test. Previously, lower contributions of the direct pathway were reported (15,39), which could be due to the metabolic characteristics of these type 2 diabetic patients (higher HbA1c and BMI) and lower insulin-to-glucagon ratios compared with the present study. In agreement with previous studies (18,19), type 2 diabetic patients also exhibited decreased net glycogenolysis and increased contribution of gluconeogenesis to glucose production during the postabsorptive period.

It is well known that EGP correlates with the degree of hyperglycemia after overnight fasting (4–8). Here we report that EGP of type 2 diabetic patients is also increased in the afternoon after a standardized breakfast and lunch, which is in contrast to normalized rates of EGP of type 2 diabetic patients after prolonged fasting (8). After dinner, EGP was rapidly suppressed in both groups but remained −0.3 mg·kg⁻¹·min⁻¹ higher during the first 3 h in type 2 diabetic patients, i.e., the maximum suppression of EGP occurs later in type 2 diabetic patients, providing for an additional ~5 g glucose released into the circulation, thus also contributing to postprandial hyperglycemia. This time course of EGP suppression is similar to previous reports (6,10,29). Earlier studies, first describing higher rates of postprandial EGP in type 2 diabetic patients (10–12), observed more pronounced defects of EGP suppression. These differences can probably be attributed to methodological uncertainties in the assessment of metabolite fluxes under rapidly changing conditions in the classic double-tracer approach, which can be reduced by the variable infusion double-tracer technique (27,29,40).

After meal ingestion, type 2 diabetic patients had lower plasma insulin but higher glucagon and FFA concentrations than CON, as previously reported (10–12,41). Increased plasma FFAs impair EGP suppression (42) and affect autoregulation of hepatic glucose metabolism (24). The molar portal vein insulin-to-glucagon ratio, as estimated from peripheral concentrations (43,44), was ~50% lower after the meal in type 2 diabetic patients. Additionally to a possible impairment of hepatic insulin sensitivity, the lower insulin-to-glucagon ratio could have contributed to the decreased net glycogen synthesis (21,23) and EGP suppression (20,45). On the other hand, type 2 diabetic patients with markedly higher postprandial insulin secre-
tion exhibit a comparable defect of EGP suppression (6). Thus, excessive postprandial hyperglycemia per se limited observed defects in hepatic glucose metabolism (46,47). Taken together, impaired net hepatic glycogen synthesis and insufficient EGP suppression resulted in decreased hepatic glucose uptake and increased amounts of glucose released into the circulation in type 2 diabetic patients.

**Hyperglycemic-hyperinsulinemic clamp conditions.** The decreased net hepatic glycogen synthesis of type 2 diabetic patients after meal ingestion can result from two distinct mechanisms: 1) decreased $V_{\text{Syn}}$ and/or 2) simultaneously increased $V_{\text{Out}}$ (21,23,48). Previous reports demonstrated that hyperglycemia per se does not markedly stimulate net hepatic glycogen synthesis, even in young healthy men (21,23). In addition, hyperinsulinemia per se is capable of stimulating hepatic glucose uptake in humans to some extent (23,25), and stepwise increases in the portal vein insulin concentration during hyperglycemia lead to an insulin concentration–dependent increase in net hepatic glycogen synthesis (21). Thus, we assumed that combined hyperglycemia and hyperinsulinemia are required to substantially stimulate net hepatic glycogen synthesis in the presence of hypoglucagonemia.

To evaluate hepatic glucose metabolism independently of type 2 diabetes–associated alterations in postprandial metabolite and hormonal responses, glycogen metabolism, as well as rates of EGP and whole-body glucose disposal, were assessed under matched conditions of hyperglycemia, portal vein insulin-to-glucagon ratios, and similar plasma FFA concentrations.

$V_{\text{SynNet}}$ values observed in CON are in line with those obtained in nondiabetic humans under similar conditions (21–23). In type 2 diabetic patients, we observed ~54% reduced rates of net hepatic glycogen synthesis. Because the $V_{\text{Out}}$ was comparable between type 2 diabetic patients and CON, the lower $V_{\text{SynNet}}$ values are entirely explained by ~46% reduced $V_{\text{Syn}}$ in type 2 diabetic patients, which under clamp conditions, cannot be explained by short-term differences in the metabolic or hormonal environment between type 2 diabetic patients and CON (Fig. 1). The comparable phosphorylase flux supports previous findings of similar hepatic glucagon sensitivity in type 2 diabetic patients and nondiabetic humans (49,50). During the hyperglycemic-hyperinsulinemic pancreatic clamp test, rates of EGP also remained higher in type 2 diabetic patients, which is in line with persistent decreased insulin sensitivity at the level of the liver (4,10).

In line with previous reports (7,26,51), HCL content was increased in type 2 diabetic patients and inversely correlated to insulin-stimulated whole-body glucose uptake during the clamp test. Furthermore, HCL content inversely correlated with $V_{\text{SynNet}}$, suggesting that HCL content can
serve as a marker not only of peripheral but also of hepatic insensitivity to insulin action.

During the clamp test, the ~40% reduction in rates of whole-body glucose uptake indicated peripheral insulin resistance in type 2 diabetic patients. Of note, $V_{\text{SynNet}}$ contributed by ~6% and ~8% to whole-body glucose disposal in type 2 diabetic patients and CON, respectively, supporting the contention that skeletal muscle accounts for ~90% of whole-body glucose disposal under clamp conditions (1). Because both glucose disposal and net hepatic glycogen synthesis were similarly decreased by 40–50% in type 2 diabetic patients of our study and skeletal muscle glycogen synthesis is reduced by 55% in type 2 diabetic patients under clamp conditions (1), glycogen synthesis seems to be equally insensitive to insulin in liver and skeletal muscle.

In contrast to current knowledge of the importance of skeletal muscle insulin resistance in the development of overt type 2 diabetic patients, there is still debate on the causality between the defects in hepatic glucose metabolism and the onset of type 2 diabetic patients. There are some arguments in favor of the hypothesis that the defects in hepatic glycogen metabolism are secondary to type 2 diabetic patients and could result from effects of acute and/or chronic hyperglycemia, increased availability of lipids, and alterations of secretion of major glucoregulatory hormones. Both the blunted rise of insulin-to-glucagon ratios and higher plasma FFA concentrations likely contributed to the impaired net hepatic glycogen synthesis in type 2 diabetic patients during the mixed-meal study. When insulin, glucagon, glucose, and FFA concentrations were successfully matched during the clamp protocol, hepatic glycogen synthesis was also impaired, indicating an additional defect aside from the effects of metabolic and hormonal differences. Moreover, the impact of chronic changes in glycemia and lipidemia, frequently termed “glucolipotoxicity,” on liver metabolism cannot be completely excluded from the results of the clamp test.

Chronically increased availability of both circulating (FFAs and triglycerides) and intracellular (HCL) lipids are frequently observed in different nondiabetic insulin-resistant populations as well as in type 2 diabetic patients (52,53) and are associated with defects in hepatic and/or whole-body glucose metabolism (26,52–55). Thus, increased HCL content in type 2 diabetic patients and its correlation with net hepatic glycogen synthesis as observed in our study indicates that fat accumulation in liver could play a role in the development of defects of hepatic glycogen metabolism in type 2 diabetic patients.

In conclusion, we show that type 2 diabetic patients exhibit a marked reduction of net hepatic glycogen synthesis after mixed-meal ingestion. Furthermore, even stimulation of glycogen synthesis by combined hyperinsulinemic hyperglycemia is unable to overcome this defect of hepatic glycogen metabolism. Thus, impaired insulin sensitivity and/or chronic glucolipotoxicity in addition to any effects of altered insulin-to-glucagon ratio or increased FFA accounts for defective hepatic glycogen metabolism in type 2 diabetic patients.

ACKNOWLEDGMENTS
The study was supported by grants from the Austrian Science Foundation (FWF; P13722-MED, P15656), the European Foundation for the Study of Diabetes (EFSDD and Novo-Nordisk Type 2 Program Focused Research Grant), the Herzfeld’sche Familienstiftung (to M.R.), Novo-Nordisk (to W.W.), and the U.S. Public Health Service (ROI DK-49230, P30 DK-45735) (to G.I.S.).

We gratefully acknowledge the cooperation of A. Hofer, H. Lentner, and G. Hofstetter (Metabolic Research Unit and Endocrine Laboratory, Department of Internal Medicine III, University of Vienna) and Professors E. Moser and S. Trattnig (MR Center of Excellence, University of Vienna).

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