Association between Hepatic Fat Accumulation and Hepatic Glucose Metabolism in Type 2 Diabetes

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Background. Postprandial hyperglycemia in type 2 diabetes mellitus (T2DM) is associated with insufficient suppression of endogenous glucose production (EGP) and impaired glycogen hepatic synthesis [1]. On the other hand T2DM often features increased hepatic fat accumulation, which has been linked to insulin resistance [2]. However, the relationship between metabolic changes and the extent of hepatic fat accumulation between T2DM and nondiabetic volunteers has not yet been fully evaluated in the postprandial like insulin stimulated state.

Aims. Thus, we measured rates of EGP, rates and pathways of hepatic glycogen synthesis and simultaneously occurring glycogenolysis and tested their association with hepatic lipid content in T2DM and healthy glucose tolerant volunteers. In order to simulate postprandial conditions we performed these studies during combined hyperglycemia and hyperinsulinemia.

Methods. Six metabolically well-controlled T2DM (5 m/1 f, age: 53±4 years, body mass index, BMI: 26.1±0.7 $kg \cdot m^{-2}$, hemoglobin A1c, HbA1c: 7.4±0.1%, known diabetes duration: 6±2 years) and 6 healthy age and BMI matched volunteers (40 m/2 f, age: 55±4 years, BMI: 27.5±0.7 $kg \cdot m^{-2}$, HbA1c: 5.4±0.1%) underwent hyperglycemic (180 mg/dL)-hyperinsulinemic (40 $mU.m^{-2}.min^{-1}$)-pancreatic clamp tests for 300 min. Hepatic glycogen concentration was measured with in vivo ^{13}C NMR spectroscopy in a 3T Medspec MR system (Bruker, Ettlingen, Germany) using a 10 cm double tuned $^{1}H/^{13}C$ surface coil and modified 1D ISIS sequence (pulse length = 225 µs, excitation angle in the coil plane 135°, NS= 2500, TR= 150 µs) [3,4] and quantified by comparison with the spectra of glycogen phantom solution. Hepatic glycogen synthesis was assessed from a linear regression of increasing hepatic glycogen concentration during [1-^{13}C]glucose labeled infusion (0-150 min) and hepatic glycogenolysis was assessed by monitoring the wash out of the ^{13}C label during subsequent non-labeled glucose infusion (150-300 min) [5,6]. Contributions of direct and indirect pathways of hepatic glycogen synthesis were assessed from the acetoaminophen-glucuronide probe and rates of EGP with the stable isotope dilution technique using [6,6-$^{2}H_2$]glucose infusion [5]. Hepatic fat content was measured by localized ^{1}H NMR spectroscopy using STEAM sequence with individual T_2 relaxation correction [2] (n $_{\text{echo time points}}$ = 5, NS= 1, TE= 11 - 70 ms, TM= 30 ms). Hepatic lipid content was quantified by integration of CH_2 and CH_3 group resonances and is expressed in arbitrary units (A.U.) as a percentage of total ^{1}H NMR signal (water + lipid). Data are given as means ± SEM. Least square linear regression and unpaired t-test were used for statistical analysis.

Results. During the pancreatic clamp tests, plasma concentrations of glucose, insulin, glucagon and free fatty acids were comparable between T2DM and CON and whole body glucose uptake was ~37% lower in T2DM (180-300 min: 8.03±0.35 vs. CON: 12.73±0.48 $mg \cdot kg^{-1} \cdot min^{-1}$; $p<0.02$). Rates of EGP were ~30% higher in T2DM before (2.38±0.10 vs. CON: 1.83±0.05 $mg \cdot kg^{-1} \cdot min^{-1}$, $p<0.01$) and during the clamp (120-300 min: 0.53±0.05 vs. CON: 0.04±0.04 $mg \cdot kg^{-1} \cdot min^{-1}$; $p<0.02$). Rates of hepatic glycogen synthesis (V_{syn}) were ~46% lower in T2DM (0.63±0.12 vs. CON: 1.17±0.15 $mg \cdot kg^{-1} \cdot min^{-1}$, $p<0.03$) with similar contribution of the direct pathway (glucose → glucose-6-phosphate → UDP-glucose) in both groups (60±10% vs. CON: 65±2%, NS). Rates of simultaneous glycogenolysis were not different (0.21±0.07 vs. CON: 0.23±0.11 $mg \cdot kg^{-1} \cdot min^{-1}$, NS) resulting in ~54% lower rates of net hepatic glycogen synthesis (Fig. 3B) in T2DM (0.42±0.10 vs. CON: 0.91±0.16 $mg \cdot kg^{-1} \cdot min^{-1}$, $p<0.03$. Hepatic lipid content before the clamp was three times higher in T2DM (9.9±2.5 A.U. vs. CON: 2.8±0.7 A.U., $p<0.05$) and negatively correlated across whole study population with rates of net hepatic glycogen synthesis during the clamp test ($R= -0.602$, $p<0.05$) as well as with the rates of whole body glucose uptake ($R= -0.576$, $p<0.05$).

Conclusions. In the condition of matched hyperinsulinemia and hyperglycemia T2DM exhibit the similar defect of hepatic glucose metabolism as during excessive postprandial hyperglycemia: (i) impaired glycogen synthesis and (ii) impaired suppression of EGP. These data suggest that hepatic glycogen synthesis of T2DM is less sensitive to insulin independently of impaired glucometabolic control or increased plasma concentrations of free fatty acids. Furthermore, our data suggest that hepatic lipid accumulation indicates impaired hepatic glucose metabolism and therefore can serve as a good marker of hepatic insulin resistance.

References:

1. Krssak M. et al. Diabetes 2002; 51 Suppl. 2: A93
2. Anderwald C. et al. Diabetes 2002; 51:3025-32
3. Rothman D. et al. Science 1991; 254:573-6
4. Bischof MG. et al. Diabetes 2001; 50:392-8
5. Cline GW. et al. J Clin Invest 1994; 94:2369-76
6. Roden M. et al. J Clin Invest 1996; 97:642-8

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