Simultaneous Changes in Liver Volume, Lipid Content and Glycogen Content in Type 2 Diabetes, Obese Subjects and Normal Controls after a Mixed Meal

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Background: Diabetes and obesity are associated with abnormalities in glucose and lipid metabolism in the fasted and post-prandial state. In health, the liver has an important role in regulating and maintaining glucose and lipid levels. This mechanism, though not completely well understood, is impaired in metabolic states such as diabetes and obesity. The aim of the study was to observe changes in hepatic lipid and glycogen in response to two mixed meals, using ^{1}H and ^{13}C MRS respectively, in four different subject groups, with varying degrees of metabolic dysfunction. Differences between the groups could provide some understanding of the disease progression of type 2 diabetes (T2DM), since it is suggested that abnormalities in lipid and glycogen metabolism are markers for the disease.

Method: 32 subjects took part in the study and were divided into four groups (group statistics given as mean ± SD). Groups were as follows: [**DMPC**] Poor Control T2DM (HbAlc>7.5%) (age=62±2years, BMI=27.8±0.5, HbAlc=7.9±0.2). [**DMGC**] Age, sex and BMI matched good control T2DM (HbAlc<7.5) (age=62±5, BMI=28.9±2.5, HbAlc=6.7±0.2). [**HO**] Age and BMI matched healthy obese (age=58±8, BMI=29.6±1.9, HbAlc=5.6±0.3). [**HNW**] Age and sex matched (to HO) healthy normal weight subjects (age=57±7, BMI=24.9±1.5, HbAlc=5.3±0.3).

Subjects underwent five sessions of MR scans during the course of the day at 0,3,5,7,and 9h, each lasting approximately 50 minutes and consisting of a liver lipid measurement (using ^{1}H MRS), a liver glycogen measurement (using ^{13}C MRS) and an image to allow quantification of liver volume. Blood samples were also taken prior to each scanning session to assess blood glucose, insulin, triglycerides and FFAs. Two standard mixed meals were given at 1 and 6h. MR sequences and parameters were as follows:

Liver Volume: T_1-weighted 3D TFE, acquired with resolution=2.08x2.08x7.00mm^3, no. slices=36, no. voxels in-plane=180x182, TR=3.11ms with total scan time (equal to breath-hold time)=14.4s. Images were analyzed by region drawing in Analyze6 to calculate liver volume.

Liver Lipid: Spectra were acquired from a PRESS localized region, TE/TR=40/5000ms, with volume=30x30x30mm^3 using respiratory gated triggering. 1024 samples were acquired with a sampling frequency =2000Hz. 32 single shot spectra were collected and were phase corrected and aligned separately in jMRUI before averaging together. Processed spectra were analyzed using an in-house Matlab programme to calculate peak areas.

Liver Glycogen: Three ^{13}C spectra were acquired using a proton-decoupled pulse acquire sequence with narrowband decoupling, sampling frequency=7000Hz, samples=512, TR=2150ms, 288 averages. Total acquisition time ~30 minutes. ^{13}C spectra were averaged and post-processed using jMRUI. Peak areas were then found using in-house software built in Matlab and were quantified using an external phantom.

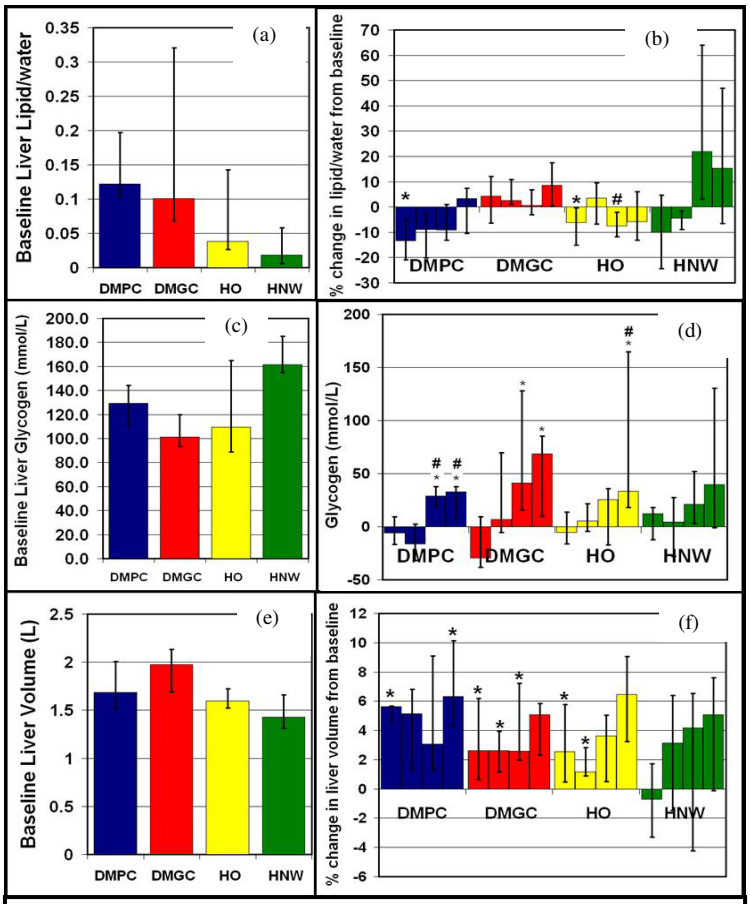

Figure 1: Plots showing (a, c and e) basal and (b, d, and f) dynamic differences from baseline (at 3, 5, 7, and 9h) in lipid/water and glycogen levels in the liver and liver volume respectively. * indicates significant ($p<0.05$) change from baseline and # indicates significant change following lunch (at t=6h).

Results: Basal levels: Liver lipid/water ratios (fig. 1a) were higher in the diabetic groups when compared to the healthy BMI matched group ($p=0.08$). The ratio was also higher in the HO group than the HNW group. In agreement with previous studies, levels of glycogen (fig. 1c) were approximately 30% lower in the HO ($p=0.2$) and DMGC ($p<0.08$) and, 20% lower in the DMPC group ($p<0.02$) when compared with the HNW group. Liver volumes were not significantly different between the groups studied, although liver volumes tended to be larger in the DM groups (fig. 1e).

Dynamic changes: Liver lipid levels (fig. 1b) tended to decrease at 2h following the breakfast, although this only reached significance in the DMPC group ($p=0.03$). Otherwise levels of lipid/water did not change significantly at any time following breakfast or lunch. In the DMPC, DMGC, and HOW groups, levels of liver glycogen (fig. 1d) tended to decrease slightly following the breakfast. In the DMPC group this decrease in glycogen continued up to the 5h point, this was in contrast with the DMGC and HO groups in which glycogen levels were increasing by the 5h measurement (although not significantly). Following the lunch, concentrations of glycogen were increased from baseline in all groups. As expected, the HNW group had the largest increased glycogen levels during the study (~70mmol/L). The levels of glycogen in the DMGC, HO and DMPC showed smaller increases from basal levels (~60, 40 and 12mmol/L respectively). Liver volume (fig. 1f) significantly increased from baseline at 3h, following the breakfast, in the DMPC ($p=0.02$), DMGC ($p=0.04$) and HO ($p=0.03$) groups and remained increased for the following 6hrs. This is in contrast to changes in the HNW group in which liver volume did not change significantly from baseline at any time point.

Discussion: Increases in liver volumes in the DMPC, DMGC and HO groups are possibly due to increases in liver water content or portal blood flow which might be reflected in decreases in liver lipid content. However, although lipid decreases initially in the DMPC group, where volume increases, changes in volume are not generally reflected in changes in lipid levels implying either that changes in liver volume may be due to other unknown sources or that they are matched by changes in liver lipid. Basal glycogen concentrations were dramatically lower in the DMPC, DMGC and HO groups relative to the HNW group. Postprandial increases in levels were also reduced and delayed in these groups, with levels rising least in the DMPC group. These are indicative of poor postprandial glycogen storage as a major feature of type 2 diabetes.

Conclusions: The high hepatic lipid levels in the diabetic groups are not explained by increased levels of obesity. However, the baseline liver glycogen levels are reduced in both diabetic groups and in the healthy obese group. Postprandial increases in liver glycogen were also attenuated in the obese and diabetic groups when compared with the healthy normal weight subjects, indicating lower ability to store ingested carbohydrate as glycogen.

References: 1. Stephenson, M. ISMRM 2008 (Toronto) #2696.

Acknowledgements: This project was funded by AstraZeneca.