Real time assessment of postprandial fat storage in liver and skeletal muscle in type 2 diabetes and in normal subjects.

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Introduction: Recent work has shown that insulin resistance in type 2 diabetes is strongly related to elevated liver and skeletal muscle triglyceride stores [1]. To understand the pathogenesis of tissue triglyceride accumulation, a method to observe real-time dynamics of postprandial liver and muscle triglyceride storage is needed. We developed a method to track the post-prandial distribution of meal derived triglycerides in the liver and muscle using ^{13}C MRS [2]. This method was used to quantify the postprandial dynamics of liver and muscle uptake in normal and type 2 diabetic subjects.

Methods: ^{13}C MRS studies were carried out on subjects with diet controlled type 2 diabetes (n=12, age 54.2 ± 2.6 years, BMI 29.8 ± 1.5 kg/m^2) and matched controls (n=8, age 49.4 ± 4.9 years, BMI 30.6 ± 1.6 kg/m^2). All subjects fasted for 12 hours prior to the start of the study. Baseline ^{13}C spectra were acquired of the calf muscle and liver and baseline-arterialised blood samples were taken. The subject was then given a standard breakfast along with 3g of 98% ^{13}C labelled algal lipid mixture (45-55% palmitic, 10-15% palmitoleic, 20-30% oleic and 10-15% linoleic acid). Additional unlabelled standard meals were given after 5 and 10 hours. Further MRS measurements of the liver were obtained at 2. 4. 6. 8$^1/_2$ and 24 hours while for the calf muscle spectra ere acquired at 5, 8 and 24 hours. Blood samples and breath samples for $^{13}CO_2$ were taken at 2, 4, 6, 8, 24 hours.
The subject was placed in a supine position in a 3T whole-body system. Two half-volume RF surface coils were used consisting of a circular ^{13}C and quadrature proton coils. The liver coil was held firmly in place with the help of a waist vest and rested across the right hypochondrium positioning the liver in the sensitive region of the coil; the calf muscle was placed directly over the muscle coil. Vacuum pillows were used to ensure accurate repositioning.
^{13}C spectra were obtained with a 100μs rectangular pulse for ^{13}C excitation, CYCLOPS phase cycling, and during acquisition broadband WALTZ-8 decoupling with a peak power of 68 ±2 W. A repetition rate of 720ms was used to allow for sufficient T_1 recovery of ^{13}C lipid magnetization and to ensure that the SAR limits were not exceeded. 1500 scans were acquired over periods of 18min for each 'time point'. All spectra were analysed using the Matlab version of the MRUI software package. Two phantoms, liver and a calf-shaped containing a 5.33 mmol/l labelled algal lipid mixture dissolved in deuterated chloroform were used to quantify incorporated labelled fatty acid concentration in liver or muscle triglyceride.

Results: Postprandial increment in ^{13}C-fatty acid content in hepatic triglyceride was rapid in both groups Fig.1A. However, the rate of increase in hepatic ^{13}C-fatty acid enrichment was significantly faster in the diabetic group compared to the control group. There was a rapid increase by 2 h in the diabetic group (6.7 ±2.6 mmol/l: p<0.03) whereas for the control group there was no significant increase (0.9 ±0.9 mmol/l). In addition, the peak increment of 10.8 ±3.4 mmol/l at 4 h was higher and seen earlier in the diabetic group than in the control group (7.3 ±1.5 mmol/l at 6 h). At peak uptake, approximately 13.3% of the meal triglyceride was stored in the liver in the diabetic group versus 9% for the control group. The mean postprandial incremental AUC of hepatic ^{13}C enrichment between the first and second meals (0 and 4 hours) was significantly higher in the diabetes group (6.1 ± 1.4 vs 1.2 ± 0.3 mmol/l/h; p< 0.02).
The mean postprandial increment in ^{13}C-fatty acid content in skeletal muscle triglyceride was rapid in the diabetic group reaching a peak increment of 1.7 ±0.9 mmol/l at 8 hours Fig. 1B. In the control group the increment was small 0.2 ±0.6 mmol/l at 5hours. The mean 24h postprandial incremental AUC of skeletal muscle ^{13}C enrichment was significantly higher in the diabetes subjects (1.7 ± 0.4 vs 0.1 ± 0.3 mmol/l/h; p < 0.01). The uptake of labelled fatty acids by skeletal muscle was small compared to the peak uptake in the liver, although this must be viewed in context of the substantial skeletal muscle mass in humans (peak storage of meal triglyceride in muscle approximately 35% and 4.3% respectively).
Both mean fasting blood glucose and plasma insulin was significantly higher in the diabetes group and remained higher throughout the study.

Conclusion: This study demonstrated the active role of both liver and muscle in handling of the postprandial tide of triglyceride in humans for the first time. The postprandial uptake into liver and skeletal muscle is increased in diabetes. This may underlie the excess tissue accretion seen in type 2 diabetes and be a primary cause of insulin resistance for glucose metabolism.

1A 1B

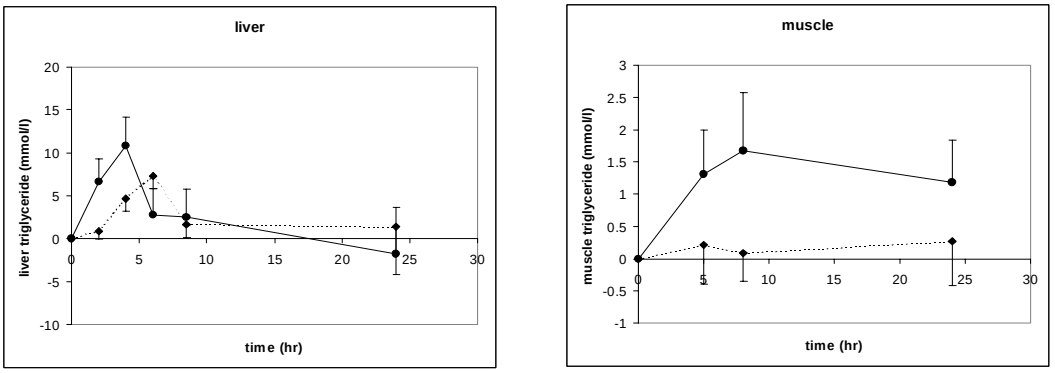

Fig. 1: Postprandial incremental change in liver triglyceride [A] and skeletal muscle triglyceride [B] in control (dashed line) and diabetic subjects (solid line). Data are shown as mean ±SE.

References
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2. Deelchand D.K., Snaar J.E.M. et al, proceedings ISMRM 2003, no.505