Variation in Skeletal Muscle and Liver Glycogen Concentration During Normal Daily Eating in Type 2 Diabetes

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Introduction
Skeletal muscle plays a major role in glucose homeostasis in normal health, with approximately 30% of meal carbohydrate being stored as muscle glycogen after the first meal of the day. Liver stores approximately 20% of meal carbohydrate after a single meal in healthy subjects. Together, the glycogen depots behave as a dynamic buffer allowing rapid storage of osmotically active glucose and maximum concentration in both muscle and liver are seen after the evening meal1,2. However, the effectiveness of this diurnal mechanism has not been previously studied in type 2 diabetes. Changes in skeletal muscle and liver glycogen concentration were measured during normal daily eating in type 2 diabetes and these values were compared to healthy glucose tolerant control data.

Methods
Type 2 diabetes subjects, mean age 62±6.1 years (n=36, 12 F and 25 M), on metformin only with HbA1c <7.6% and healthy volunteers (n=6, 4 F and 2 M) matched for weight, Body mass index (BMI), age and sex were recruited after obtaining informed consent. Volunteers were encouraged to maintain normal diet and exercise routine for 3 days prior to assessment. 1H-decoupled 13C spectra were acquired to measure glycogen in calf muscle and liver glycogen in the fasting state (08:30h) and at 20:00h after three defined meals (60% carbohydrate, 20% protein, 20% fat). Spectra were acquired on a 3T Achieva whole body scanner (Philips, Best, The Netherlands) equipped with a PulseTeq 13C/1H leg coil and a home-built 13C/1H liver coil (13C coil diameters = 6cm and 12cm respectively). Figure 1 shows the custom 13C/1H coil constructed for human liver spectroscopy studies. Glycogen content was determined from the magnitude of natural abundance C1-glycogen signal at 100.5 ppm, quantitation was performed by comparison of peak magnitudes to spectra from leg- and liver-shaped phantoms containing glycogen solutions of known concentrations. All data were analysed with jMRUI software.

Results
In the Type 2 Diabetic subject group, the mean fasting blood glucose was 7.8±1.0 mM (compared to 5.2±0.6 mM (p<0.0001) for the control group), HbA1c was 6.4±0.5% and BMI 29.7 ±3.4kg/m2. Fasting muscle glycogen was 68.9±17.1 mmol/l, and there was a complete lack of increase over the day of eating, as shown in Figure 3. A typical post meal 13C spectrum acquired from the calf a healthy volunteer is shown in Figure 2. The C1 resonance of glycogen can be clearly seen at 100.5 ppm (circled). In the control group, muscle glycogen increased by more than 30% post-meal compared to fasting levels 61.7±16.9 mmol/l. There was a significant difference between Type 2 Diabetic post-meal glycogen levels compared to control data (p=0.006).
In the Type 2 Diabetic patients, fasting liver glycogen was 296.1±95.9mmol/l, and there was a small increase (18%) in glycogen content post meal, Figure 4. A similar 17% increase was found between fasting glycogen levels for the control group (307.8±109.6mmol/l) and post meal glycogen content, 358.7±97.1mmol/l.

Discussion
Unlike glucose tolerant controls, in Type 2 diabetes, skeletal muscle does not contribute significantly to the storage of glucose during diurnal food intake. The liver makes a similar contribution to glucose storage in both Type 2 Diabetes and healthy controls during diurnal food intake. The failure of the buffering capacity of skeletal muscle glycogen stores during diurnal eating in Type 2 Diabetes contributes to post-prandial hyperglycaemia.

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References