Investigating the pathophysiology of type 2 diabetes: a cross-sectional study of fat distribution in liver, pancreas, serum and adipose tissue

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1. Introduction

Type 2 diabetes (T2D) is a chronic disease of metabolic dysfunction which carries a high burden of morbidity and mortality. Recent studies which demonstrate reversibility in T2D have given insights into the pathophysiology of T2D, but the aetiological mechanisms are still unclear. As individuals lose weight and return to normal glucose tolerance, pancreas fat reduces[1], yet a relationship between pancreas fat and development of T2D has not yet been elucidated.

Pancreas fat is an emerging research area in type 2 diabetes and novel techniques allow us for the first time to accurately measure pancreas fat *in vivo*[2].

One hypothesis speculates that chronic calorie surfeit in individuals with pre-existing peripheral insulin resistance leads to fat accumulation in the liver, causing hepatic overproduction of very low density (VLDL) triglycerides which travel through the bloodstream to be deposited in the pancreas where they are toxic to insulin-secreting beta cells[3] (**Figure 1, orange boxes, dark arrows**).

This study aims to provide associations between liver and pancreas fat, adipose tissue and serum VLDL triglycerides in a large cohort of humans with and without T2D in order to support or refute this hypothesis.

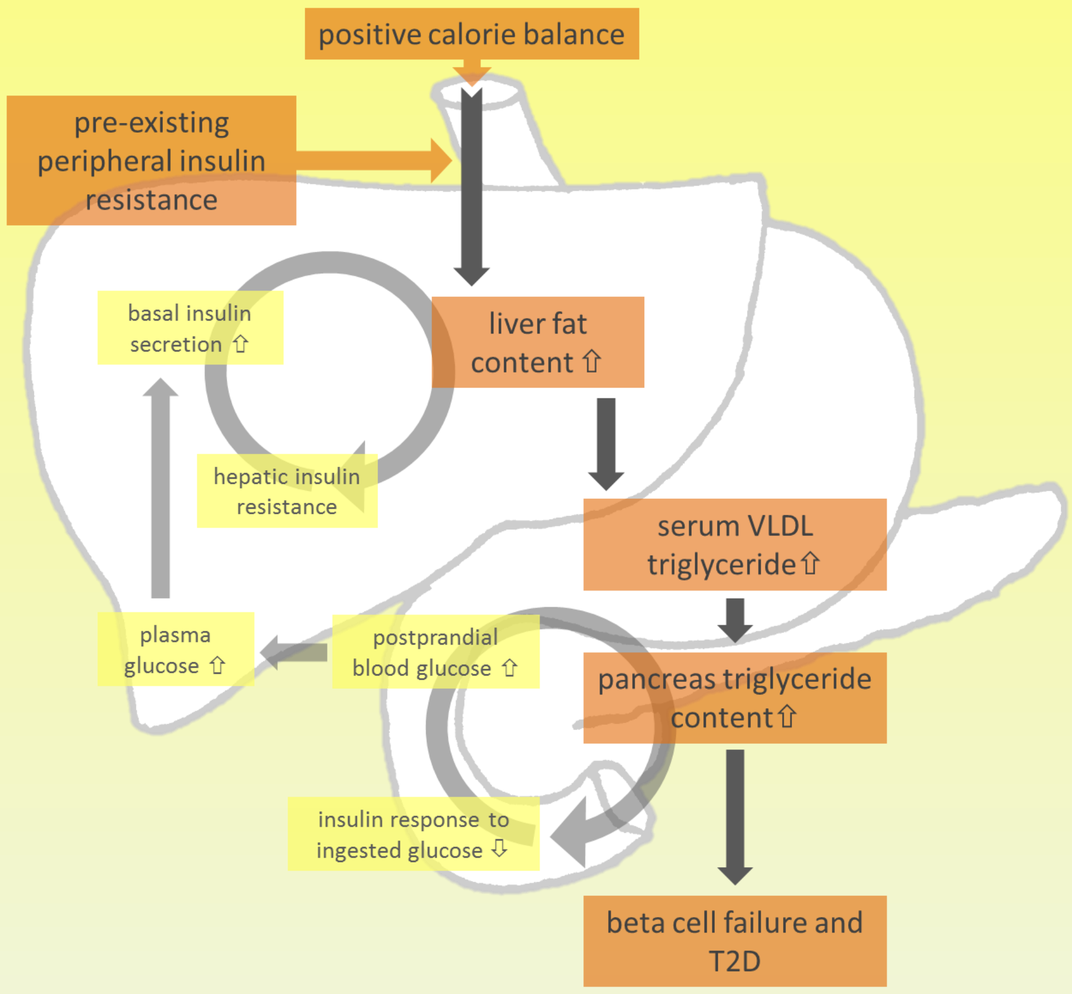

Figure 1: Schematic representation of the two-cycle hypothesis of aetiology of type 2 diabetes. Adapted from Taylor[1]. T2D = type 2 diabetes

2. Methods

T2D was diagnosed using World Health Organisation / International Diabetes Federation criteria[4].

Liver and pancreas fat were measured using magnetic resonance imaging (MRI) with a 3.0T Philips Achieva scanner (Philips, Best, the Netherlands) with a 3-Point Dixon imaging sequence for fat and water separation[2]. Regions of interest (ROIs) were selected on each image and intensity of signal within each ROI converted into a fat percentage value.

Body fat was measured using air displacement plethysmography (BOD POD Express; Life Measurement, Concord, CA, USA).

Serum VLDL triglycerides were measured by lipase with released glycerol by a Roche Cobas centrifugal analyser using a colorimetric assay (ABX Diagnostics, Montpellier, France).

Data were analysed using SPSS Statistics 19.0 software (IBM Corporation, Armonk, NY, USA).

3. Results

Baseline data were obtained from participants enrolled in three interventional studies. Participants with T2D (n=71, 63% male, HbA1c 47±5mmol/mol) had a disease duration of <15 years and controlled their T2D with diet ± metformin ± sulfonylurea only. In those without T2D (n=9), 78% were male.

Groups with and without T2D were matched for weight (96.3 [83.2-110.0] versus 104.8 [99.7-113.7]kg, p=0.56). Those with T2D were older (57.0 [51-63] versus 47.5 [44-52] years), had a lower BMI (33.1 [29.2-39.5] versus 37.0 [33.0-42.0]) and lower body fat (35.5 [26.8-42.9] versus 47.1 [32.5-49.3]%), p<0.05.

Liver fat (7.2 [3.9-10.5] versus 6.1 [4.1-13.4]%, p=0.77), pancreas fat (5.5 [4.5-6.7] versus 4.9 [3.7-7.7]%, p=0.50) and serum triglycerides (1.55 [1.09-1.82] versus 1.50 [1.10-1.85] mmol/L, p=0.88) were not different between those with and without T2D.

Serum triglycerides were not associated with body fat percentage in the T2D (r_s=0.08, p=0.51) or no T2D (r_s=-3.93, p=0.12) groups. Within all participants serum VLDL triglycerides increased with liver fat (r_s=0.489, p<0.01). Pancreas fat displayed no relationship with liver fat (r_s=0.017, p>0.05) or serum VLDL triglycerides (r_s=-0.94, p>0.05). These associations endured when data were analysed taking diabetic status into account and when serum triglyceride levels were categorised (**Figure 2**).

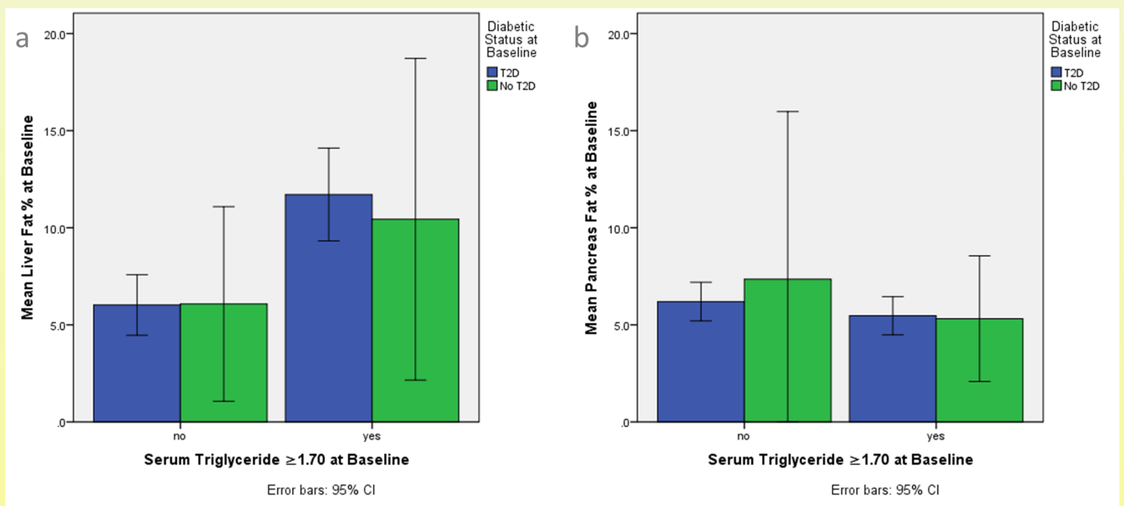

Figure 2: Liver fat was greater in hypertriglyceridaemia with and without T2D than in normotriglyceridaemia, p=0.00 for all participants and T2D group, NS for No T2D group **(a)**. The same relationship was not evident between pancreas fat and hypertriglyceridaemia, p>0.05 for both groups **(b)**.

4. Discussion

In this cohort liver fat, pancreas fat and serum triglycerides could not be used to discriminate between those with and without T2D. A dose-response relationship between pancreas fat and beta cell function could not be seen, suggesting that if the mechanism of T2D is via toxicity of circulating VLDL triglycerides to beta cells then there must be some susceptibility factor in affected individuals.

The groups were not matched for age, sex or body fat and the non-diabetic group was of small size, and these factors likely influence the results. Nonetheless the non-diabetic group had higher liver and pancreas fat and serum VLDL triglyceride levels, suggesting that these variables alone cannot account for the pathophysiology of T2D.

MRI cannot differentiate between extracellular (adipocyte) and intracellular (beta cell) lipid—this may be an important distinction to be made in relation to beta cell toxicity. Development of a non-invasive in vivo method of measuring these two sources of pancreas fat is required in order to fully define the possible pathophysiological role of this fat depot in T2D.

5. References

1 Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC & Taylor R (2011) Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglyerol. *Diabetologia* (54); pp.2506-2514

2 Kovanlikaya A, Guclu C, Desai C, Becerra R & Gilsanz V (2005) Fat quantification using three-point Dixon technique: in vitro validation. *Academic Radiology* (12); pp.636-639.

3 Taylor R (2013) Type 2 diabetes: etiology & reversibility. *Diabetes Care* (36); pp.1047-55

4 WHO & IDF (2006) Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia: Report of a WHO/IDF consultation. Geneva: WHO