Reversal of type 2 diabetes is associated with decrease in pancreas and liver fat

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Introduction: Type 2 diabetes has long been regarded as a chronic progressive condition, capable of amelioration but not cure. A steady rise in plasma glucose occurs irrespective of degree of control or type of treatment [1]. However, type 2 diabetes is clearly reversible following bariatric surgery [2]. The effect on plasma glucose follows within days of surgery and since weight loss has not occurred by then it has become assumed that gastrointestinal surgery produces direct effects upon secretion of incretin hormones [3,4]. Nonetheless, the extent of change in incretins after gastric bypass surgery is modest and not consistently seen in type 2 diabetes [5,6,7]. We have previously hypothesized that the profound effect of sudden negative calorie balance on metabolism could entirely explain the post-bariatric surgery effect, via decrease in the intra-cellular fatty acid levels in liver and pancreas [8]. This study was designed to test the hypothesis that type 2 diabetes is reversible by acute negative calorie balance alone and additionally to establish the pathophysiologic basis of any return to normal blood glucose control. We examined specifically the restoration of first phase insulin response and normalisation of hepatic insulin sensitivity in association with decrease of fat content in pancreas and liver.

Methods: 11 subjects with type 2 diabetes were recruited (9 male, 2 female, age 49.4±2.5y,HbA_{1C} 6.5-9.0%, diabetes duration < 4 years, on diet alone, metformin or sulfonylurea, stable BMI 25-45 kg/m^2). Subjects were excluded if treated with thiazolidinediones, insulin, steroids or beta blockers, serum creatinine > 150 mmol/l, serum alanine transaminase > 2.5 fold above upper limit, or if there were contraindications to MRI. Two subjects were on diet alone, seven were on metformin and two subjects were on sulfonylureas. Subjects discontinued sulfonylurea two months before the baseline study or metformin one week before the baseline study. A group of nine control subjects was matched for weight, age and sex. These subjects had no family history of diabetes nor were taking any medication known to affect glucose tolerance or insulin sensitivity and normal glucose metabolism was confirmed by a standard oral 75g glucose tolerance test. The study was approved by the Local Ethics Committee, and all subjects gave informed consent. Four further subjects failed to comply with the diet. Assessment of liver and pancreas fat content by MRI, insulin sensitivity (by measuring hepatic glucose production during an isoglycaemic-hyperinsulinaemic clamp [9]) and beta cell function was carried out on 4 occasions in subjects with type 2 diabetes: at baseline immediately prior to the hypocaloric period, and after 1, 4 and 8 weeks of the very low calorie diet (VLCD). Control subjects did not undertake the diet. The VLCD consisted of a liquid diet formula (46.4% carbohydrate, 32.5% protein and 20.1% fat; plus vitamin, minerals and trace elements; 510kcal/day; Optifast; Nestle Nutrition, UK), supplemented with 3 portions of non-starchy vegetables such that total energy intake was between 600-800 kcal/day. Subjects were encouraged to drink at least 2 L water each day and asked to maintain their habitual physical activity. Support was provided by regular telephone contact. The fat content in the liver and pancreas was assessed using a 3 point Dixon technique. A Philips 3.0T Achieva scanner and 6-channel cardiac coil were used to acquire three gradient echo scans with adjacent out-of-phase and in-phase echoes (TR/TE/averages/flip angle=50ms/3.45,4.60,5.75ms/1/30º, matrix 160x109, FOV 400-480mm to suit subject size with 70% phase FOV). 6 slices were acquired within a 17 second breath-hold to cover the liver with slice thickness 10mm and pancreas with slice thickness 5mm. The data was analyzed in MATLAB to produce separate fat and water images [10]. The fat content of the image was expressed as a percentage of the total signal per voxel. The fat percentage in the liver and pancreas was evaluated with five liver ROIs and two pancreas ROIs were defined and averaged in a blinded fashion by one observer (KGH), avoiding contamination from blood vessels, gallbladder and visceral fat: pancreas ROIs defined the body and tail of the pancreas. Image-based measurements help ensure that visceral fat cannot contribute to pancreatic fat measurements. The inter-scan repeatability coefficients were 0.5% for the liver and 0.9% for the pancreas.

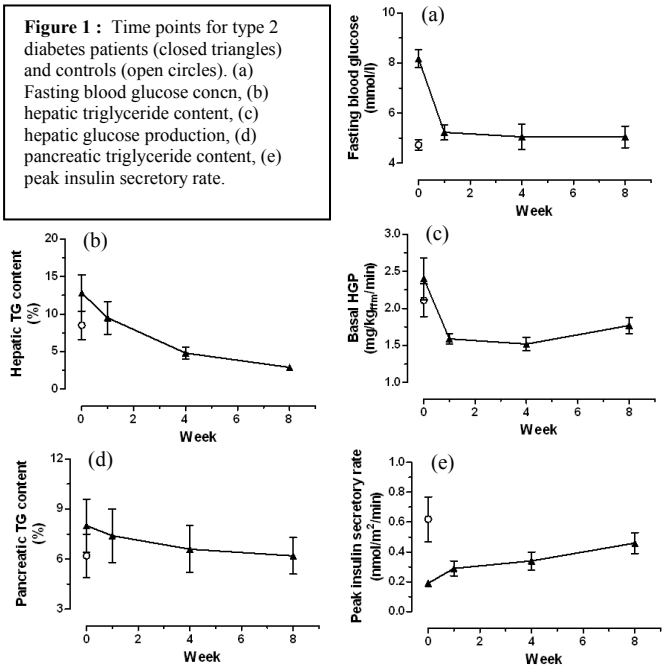

Figure 1 : Time points for type 2 diabetes patients (closed triangles) and controls (open circles). (a) Fasting blood glucose concn, (b) hepatic triglyceride content, (c) hepatic glucose production, (d) pancreatic triglyceride content, (e) peak insulin secretory rate.

Table 1 : Subject characteristics - * = significant change from baseline

	Control	T2DM			
	Baseline	Baseline	1 week	4 weeks	8 weeks
Weight (kg)	101.5±3.4	103.7±4.5	99.7±4.5*	94.1±4.3*	88.4±4.3*
BMI (kg/m^2)	33.4±0.9	33.6±1.2	32.3±1.2*	30.5±1.2*	28.7±1.3*
Pl. insulin (mU/l)	16.6±3.9	21.7±4.5	10.6±1.5*	10.3±1.6*	8.3±1.6*
TG (mmol/l)	1.8±0.1	2.4±0.5	1.2±0.1*	1.0±0.1*	1.3±0.3*

Results: Average weight loss during the 8 weeks of VLCD was 15.3 ± 0.7 kg, or 15 ± 1% (**Table 1**). Weight loss was greatest during the first week at 3.9 ± 0.2 kg. After 1 week of negative calorie balance fasting blood glucose decreased from 8.2 ± 0.4 to 5.2 ± 0.3 mmol/l (p = 0.003; **figure 1a**) and was not significantly different to that of the non-diabetic control group (4.7±0.1 mmol/l; p=0.18). It remained stable for the rest of the 8 week study (5.1± 0.1mmol/l at weeks 4 and 8; p=0.52 compared with control). Hepatic TG content was 12.8 ± 2.4% in the diabetic group compared to 8.5 ± 1.9% in the control group (p = 0.14). Hepatic TG content decreased by 30±5% during the first week, becoming similar to control values (p=0.75, **figure 1b**). Over the 8 week study period it continues to decline to within the non-obese normal range (2.9 ± 0.2%, p = 0.003; **figure 1b**). This represented a 70 ± 5% reduction during study period. Hepatic insulin resistance decreased markedly across this period (**figure 1c**). Pancreatic TG content was 8.0 ± 1.6% in the diabetic group compared to 6.0 ± 1.3% in the control group (p = 0.17). During the 8 weeks of VLCD, pancreatic fat content decreased from 8.0 ± 1.6% to 6.2 ± 1.1% (p = 0.03, **figure 1d**). During the insulin secretion test the planned step increases in plasma glucose levels of +2.8 and +5.6 mmol/l were achieved (Figures 3a). In the diabetes subjects, peak ISR at 6 minutes was minimal at baseline and was at 1 week (0.19±0.02 vs. 0.29±0.05 nmol/min/m^2; p=0.20). The first phase insulin response steadily increased and was highly significant by 8 weeks (0.34±0.06 and 0.46±0.07 nmol/min/m^2.at 4 and 8 weeks; p=0.09, p=0.006 respectively). The ISR at 8 weeks in the diabetes subjects was not significantly different to control values (0.46±0.07 vs. 0.62±0.15; p=0.42, **figure 1e**). Maximal insulin response, reflected by the area under the arginine peak, was 58% lower in the diabetes subjects at baseline. There was a modest increase after 1 week (7.00±1.02; p=0.52) and at 8 weeks the maximum insulin response had increased to 91% of the control values (9.18±1.47; p<0.05 vs. baseline; p=0.63 vs. controls).

Conclusion : The present demonstration that both the defect in insulin secretion and the defect in hepatic insulin action which characterise type 2 diabetes are reversed in step with decrease of fatty acid-triglyceride in pancreas and liver respectively is of great importance in understanding the condition. This new insight allows understanding of the behaviour of type 2 diabetes in populations as well as at the individual level. It carries major implications for the information to be given to those diagnosed with type 2 diabetes, who should be informed that they have a potentially reversible condition, not one which is inevitably progressive.

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