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Preoperative β-cell function in patients with type 2 diabetes is important for the outcome of Roux-en-Y gastric bypass surgery

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Key points

- Roux-en-Y gastric bypass surgery leads to remission of type 2 diabetes in the majority of patients suffering from the disease.
- The gut hormone glucagon-like peptide-1 is believed to be of major importance for the remission process.
- The present project demonstrates a marked difference in the chance of remission of type 2 diabetes in patients with low or high preoperative β-cell function in spite of a similar post-surgery increase in postprandial glucagon-like peptide-1 release.
- Furthermore, post-surgery intravenous glucose administration, which does not stimulate release of glucagon-like peptide-1, leads to increased insulin secretion in the patients with the best preoperative β-cell function.
- Together the present findings indicate that patients with type 2 diabetes with high preoperative β-cell function experience a glucagon-like peptide-1-independent increase in β-cell function after gastric bypass surgery.

Abstract The majority of the patients with type 2 diabetes (T2DM) show remission after Roux-en-Y gastric bypass (RYGB). This is the result of increased postoperative insulin sensitivity and β-cell secretion. The aim of the present study was to elucidate the importance of the preoperative β-cell function in T2DM for the chance of remission after RYGB. Fifteen patients with and 18 without T2DM had 25 g oral (OGTT) and intravenous (IVGTT) glucose tolerance tests performed at inclusion, after a diet-induced weight loss, and 4 and 18 months after RYGB. Postoperative first phase insulin secretion rate (ISR) during the IVGTT and β-cell glucose sensitivity during the OGTT increased in T2DM. Postoperative insulin sensitivity and the disposition index (DI) markedly increased in both groups. By stratifying the T2DM into two groups according to highest ($T2DM_{high}$) and lowest ($T2DM_{low}$) baseline DI, a restoration of first phase ISR and β-cell glucose sensitivity were seen only in $T2DM_{high}$. Remission of type 2 diabetes was 71 and 38% in $T2DM_{high}$ and $T2DM_{low}$, respectively. Postoperative postprandial GLP-1 concentrations increased markedly, but did not differ between the groups. Our findings emphasize the importance of the preoperative of β-cell function for remission of diabetes after RYGB.

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Abbreviations AUC, area under the curve; BMI, body mass index; DI, disposition index; FFA, free fatty acids; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin A1c; HOMA-IR, homeostatic model assessment of insulin resistance; ISR, insulin secretion rate; IVGTT, intravenous glucose tolerance test; OB, obese patient without type 2 diabetes; OGTT, oral glucose tolerance test; RYGB, Roux-en-Y gastric bypass; T2DM, patient with type 2 diabetes.

Introduction

β-Cell dysfunction and insulin resistance are key features of type 2 diabetes. When pancreatic β-cells can no longer secrete the insulin required to meet the insulin demand, hyperglycaemia develops. Today Roux-en-Y gastric bypass (RYGB) is widely used as an effective treatment for both obesity and type 2 diabetes. The procedure results in loss of ∼60% of excess weight (Buchwald *et al.* 2009), and the majority of the patients with type 2 diabetes experience a rapid improvement in glycaemic control, often leading to long lasting remission of the disease (Sjostrom, 2013). This makes RYGB superior to the current optimal medical treatment for diabetes (Mingrone *et al.* 2012; Schauer *et al.* 2012, 2014).

The remission process of type 2 diabetes following RYGB has been intensively studied in the last few years. The fasting endogenous glucose production decreases, and the suppression may be stronger after surgery (Camastra *et al.* 2011; Dunn *et al.* 2012; Jacobsen *et al.* 2012; Bojsen-Moller *et al.* 2014), and as body and fat mass decrease, insulin-mediated whole body glucose uptake increases (Campos *et al.* 2010; Kashyap *et al.* 2010; Camastra *et al.* 2011; Bojsen-Moller *et al.* 2014). In combination, these changes alone may improve glycaemic control, but in addition a major increase in postprandial glucagon-like peptide-1 (GLP-1) plasma concentration is a constant finding after RYGB (le Roux *et al.* 2007; Laferrere *et al.* 2007, 2008; Morinigo *et al.* 2006; Bose *et al.* 2010; Jorgensen *et al.* 2012; Salinari *et al.* 2013; Bojsen-Moller *et al.* 2014). GLP-1, along with the other incretin hormone, glucose-dependent insulinotropic polypeptide (GIP), potentiates the glucose-induced insulin secretion (known as the incretin effect), and this contributes to the improved postprandial insulin secretion and glucose disposal. In support of this notion, it has been shown that the incretin effect is increased in patients with type 2 diabetes after RYGB (Laferrere *et al.* 2007), and that blockade of the GLP-1 receptor abolishes the improved glucose homeostasis after surgery (Salehi *et al.* 2011; Jorgensen *et al.* 2013). Recently Salinari *et al.* (2013) showed that the insulin secretion rate (ISR) was increased in patients with type 2 diabetes 1 month after RYGB only when glucose was administered orally and not intravenously. Since the incretin hormones are only stimulated when glucose is ingested orally, this result further supports the role of GLP-1 in the rapid post-operative restoration of the β-cell function. However, in a recent study by Vetter *et al.* (2014), a similar improvement in β–cell function was seen in two groups of patients with type 2 diabetes, who had a matched diet or RYGB induced weight loss. Furthermore, the deterioration in β-cell function was similar in the two groups when exendin-9, a GLP-1 receptor antagonist, was administered (Vetter *et al.* 2014). Thus, factors apart from GLP-1 must also influence the postoperative restoration of the β-cell function in patients with type 2 diabetes.

The aim of the present study was to investigate β-cell function in morbidly obese patients with and without type 2 diabetes before and 4 and 18 months after RYGB. To elucidate the role of the increased postoperative GLP-1 release, the β-cell function was tested after both oral and intravenous glucose administration. Subsequently, the patients with type 2 diabetes were stratified into two sub-groups with respect to their preoperative β-cell function in order to elucidate how this parameter affected their post-operative remission. We hypothesized that β-cell function in general would improve after surgery, and primarily when glucose was given orally. In addition, we hypothesized that a better β-cell function prior to surgery would predict a better postoperative recovery of the β-cells and thereby improve the chance of remission.

Methods

Thirty-three patients were recruited, 15 with type 2 diabetes (T2DM) and 18 without (OB), scheduled for a Roux-en-Y gastric bypass surgery procedure. Patient characteristics are shown in Table 1. Inclusion criteria followed the Danish gastric bypass surgery guidelines (prior to January 2011): age 18–60 years, body mass index (BMI) >40 kg m^{-2} or BMI >35 kg m^{-2} with obesity-related co-morbidities (e.g. type 2 diabetes). Exclusion criteria were known cardiovascular disease, polycystic ovary syndrome, dysregulated hypertension, thyroid disease and other diseases demanding medication known to affect the test results. Remission of diabetes

Table 1. Subject characteristics in T2DM and OB

	OB				T2DM				Statistics		
	A	B	C	D	A	B	C	D	Group	Time	G × T
n	18	18	18	13	14	13	15	12			
Sex (M/F)	3/15				6/9						
Age (years)	36 ± 2				42 ± 1				0.02		
Weight (kg)	129 ± 5	123 ± 4†	101 ± 4†	90 ± 5†	123 ± 5	119 ± 5†	98 ± 4†	90 ± 6†	0.91	< 0.001	0.18
Weight loss (%)		5 ± 1	22 ± 1†	32 ± 2†		5 ± 1	22 ± 1†	29 ± 2†	0.31	< 0.001	0.42
BMI (kg m^{-2})	43 ± 1	41 ± 1†	33 ± 1†	30 ± 1†	42 ± 1	41 ± 1†	33 ± 1†	30 ± 1†	0.88	< 0.001	0.07
Fasting insulin (pmol l^{-1})	96 ± 10	76 ± 11†	40 ± 6†	29 ± 3‡	120 ± 15	101 ± 9†	47 ± 8†	46 ± 7‡	0.02	< 0.001	0.06
Fasting C-peptide (pmol l^{-1})	734 ± 47	647 ± 60	558 ± 73‡	365 ± 29‡	701 ± 47	721 ± 46	493 ± 36‡	449 ± 34‡	0.73	< 0.001	0.36
Fasting glucose (mmol l^{-1})	5.5 ± 0.1	5.3 ± 0.1	5.1 ± 0.1‡	5.0 ± 0.1‡	7.9 ± 0.6	7.4 ± 0.3	6.4 ± 0.5‡	5.8 ± 0.4‡	< 0.001	< 0.001	0.06
FFA (μmol l^{-1})	675 ± 36	698 ± 37	649 ± 33	538 ± 45†	649 ± 34	640 ± 41	577 ± 45	503 ± 30†	0.21	< 0.001	0.86
Cholesterol (mmol l^{-1})	4.2 ± 0.2	4.0 ± 0.1	3.5 ± 0.1‡	3.5 ± 0.2‖	3.7 ± 0.3	3.6 ± 0.2	3.1 ± 0.2‡	3.6 ± 0.2‖	0.07	< 0.001	0.13
Glycerol (μmol l^{-1})	86 ± 4	84 ± 6	81 ± 6	67 ± 6†	72 ± 6	65 ± 5	63 ± 7	52 ± 2†	0.007	0.002	0.95
HbA1c (mmol mol^{-1})	37 ± 1*	36 ± 1*	35 ± 1*	36 ± 1	55 ± 4	48 ± 3†	42 ± 2‡	40 ± 3‡	—	—	< 0.001
HbA1c (%)	5.5 ± 0.1*	5.4 ± 0.1*	5.3 ± 0.1*	5.4 ± 0.1	7.2 ± 0.3	6.5 ± 0.3†	6.0 ± 0.2‡	5.8 ± 0.2‡	—	—	< 0.001
Matsuda index (a.u.)	2.2 ± 0.2	2.6 ± 0.3	3.7 ± 0.4‡	6.3 ± 0.4‡§	1.6 ± 0.2	1.8 ± 0.2	3.8 ± 0.5‡	4.0 ± 0.6‡	—	—	0.01
HOMA-IR (a.u.)	1.8 ± 0.2	1.4 ± 0.2†	0.8 ± 0.1‡	0.6 ± 0.1‡	2.3 ± 0.3	2.0 ± 0.2†	0.9 ± 0.1‡	0.9 ± 0.1‡	0.02	< 0.001	0.07
DI_{OGTT} (a.u.)	5.0 ± 1.7	4.2 ± 0.6	4.9 ± 0.6‡	6.5 ± 1.1‡	0.5 ± 0.1	0.9 ± 0.3	1.4 ± 0.4‡	2.2 ± 0.8‡	< 0.001	< 0.001	0.17
DI_{IVGTT} (a.u.)	1.9 ± 0.3	2.3 ± 0.3	2.7 ± 0.3‖	3.8 ± 0.3‖	0.3 ± 0.1	0.6 ± 0.3	1.9 ± 0.5‖	2.1 ± 0.7‖	< 0.001	0.004	0.37
Diabetes (HbA1c > 42.1 mmol mol^{-1}, fasting glucose > 5.6 mmol l^{-1} or medication)					14	12	10	4			
Time since diagnosis (years)					5.2 ± 2						
Medication (no. of patients)											
Antihypertensive	2	2	2	2	7	6	4	4			
Statins					2	2	2	2			
Metformin					7	7	1	1			
Insulin					4	4	0	0			
GLP-1 analogue					4	4	0	0			
DPP-4 inhibitor					1	1	0	0			

A: baseline; B: after a diet-induced weight loss; C: 4 months after RYGB; D: 18 months after RYGB. FFA: free fatty acids; HbA1c: glycosylated haemoglobin, type A1c; DI_{OGTT}: disposition index calculated from the OGTT; DI_{IVGTT}: disposition index calculated from the IVGTT; HOMA-IR: homeostatic model assessment of insulin resistance. *Significantly different from T2DM; †significantly different from previous examinations; ‡significantly different from preoperative values; §significantly different from C; ‖significantly different from A. Data are means ± SEM.

after RYGB was defined as glycosylated haemoglobin type A1c (HbA1c) <42.1 mmol mol^{-1}, fasting glucose <5.7 mmol l^{-1} and no medication.

Before enrollment subjects gave their informed signed consent. The study was approved by the Ethical Committee of Copenhagen (journal no. H-C-2009-050) and performed according to the *Declaration of Helsinki*. The present study is part of a larger project (GASMITO) investigating the metabolic and psycho-social effects of gastric bypass surgery. Results from other parts of the project have previously been published (Wimmelmann *et al.* 2014*a*,*b*).

Each patient was examined four times. The first examination was at baseline (A) and the second after a preoperative diet-induced weight loss just prior to surgery (B). Examination A and B were separated by 64 ± 8 days. Examination C was performed 4.5 ± 0.1 months and examination D 18.6 ± 0.8 months after RYGB when patients were weight stable. Each examination included an oral (OGTT) and an intravenous glucose tolerance test (IVGTT) and measurement of the body composition. Subjects were asked not to perform vigorous exercise the day before a test. GLP-1 analogues were paused 2 days before a test and any other medication (Table 1) 1 day before. Seven (5 OB, 2 T2DM) subjects only performed the IVGTT protocol. A few patients did not complete all four tests due to technical difficulties in getting venous access, one patient could not complete the study due to complications after the RYGB procedure and one patient became pregnant before her last examination (Table 1). Twelve OB and 10 T2DM completed all four tests. All patients completed at least one experiment prior to surgery.

Oral- and intravenous glucose tolerance test

Subjects reported to the laboratory after an overnight fast and a catheter was inserted in a cubital vein. Baseline blood samples were drawn, and 25 g glucose dissolved in

200 ml of water was ingested in 1 min. After ingestion blood samples were drawn every 30 min during the following 2 h, and plasma concentrations of metabolites, insulin, C-peptide, GLP-1 and GIP were determined. A dual-energy x-ray absorptiometry scan was performed to determine changes in fat mass, fat free mass and bone mass (GE Medical Systems, Lunar iDXA Series, Madison, WI, USA). On a separate day, subjects reported to the lab after an overnight fast and a catheter was placed in a cubital and in a dorsal vein of the hand, which was placed in a heating pad to provide arterialized blood. Baseline blood samples, including a sample for HbA1c measurement, were drawn and 25 g of glucose dissolved in 137 ml of saline (0.9%) was infused during 1 min. Blood samples were drawn frequently for 40 min, and plasma concentrations of glucose, insulin and C-peptide were determined. The OGTT and IVGTT were separated by at least 48 h.

Biochemistry

Blood samples for glucose, free fatty acids (FFA) and glycerol analyses were collected into EDTA-containing tubes during the OGTT and samples for glucose were collected into BD (Becton, Dickinson and Co., NJ, USA) sodium fluoride- and EDTA-containing tubes during the IVGTT. Blood samples for plasma cholesterol analysis were collected into heparinized tubes. Blood samples for insulin, C-peptide, GIP and GLP-1 analysis were collected into BD aprotinin-containing Vacutainers. All samples were immediately cooled to 4°C and centrifuged at 2000 *g* for 10 min whereafter plasma was collected and stored at –80°C until time of analysis.

Plasma glucose, FFA, glycerol and cholesterol were measured on a Hitachi Cobas 6000 chemistry analyser (Roche A/S, Hvidovre, Denmark). Insulin and C-peptide were assessed using commercial ELISA kits (insulin: Dako A/S, Glostrup, Denmark, cat. no. K6219. C-peptide: ALPCO Diagnostics, Salem, HN, USA, cat. no. 80-CPTHU-E01.1, E10). Samples were analysed on a Multiskan FC Microplate Photometer (Thermo Fisher Scientific, Slangerup, Denmark). Plasma for total GLP-1 and total GIP was extracted with 70% ethanol (vol/vol, final concentration) before measurement. GLP-1 was measured using antibody no. 89390 (Orskov *et al.* 1994), which is specific for the amidated C-terminus. GIP was measured using antibody 80867, which is specific for the C-terminus (Lindgren *et al.* 2011). Assay sensitivities were below 2 pmol l^{-1}. Intra-assay coefficient of variation was below 6% at 20 pmol l^{-1}, and recovery of standard, added to plasma before extraction, about 100% when corrected for losses inherent in the plasma extraction procedure. All samples were analysed in duplicate.

Calculations and statistical analysis

To investigate systematic effects of group (T2DM and OB), time (A, B, C and D) and possible interactions (group × time), a mixed model ANOVA (autoregressive correlation structure) with least squares *post hoc* test followed by a Tukey–Kramer adjustment was performed. Satterthwaite approximation was used in case of missing values. Data that were not normally distributed or had unequal variance were log-transformed before statistical analyses. Hormone concentrations during the OGTTs and IVGTTs were calculated as area under the curve (AUC) using the trapezoidal rule, and reported as change from baseline (incremental change). Reporting incremental AUCs allows us to compare a hormone response to glucose without the potential confounding effect of a change in the fasting hormone concentration during the study. Since the postprandial plasma GLP-1 concentration decreased during the OGTT at examination A the incremental AUC is negative. The insulin secretion rate (ISR) was calculated, using the ISEC software program (Hovorka *et al.* 1996) by deconvolution of C-peptide concentrations and using population-based estimates of C-peptide kinetics. The β-cell glucose sensitivity was calculated as the slope of the ISR curve *vs.* the prevailing plasma glucose concentration during the OGTT. The Matsuda index, calculated from OGTT data as: $10.000 \times (\sqrt{(\text{fasting glucose} \times \text{fasting insulin} \times \text{mean glucose} \times \text{mean insulin})})^{-1}$, was used as an index of insulin sensitivity (Matsuda & Defronzo, 1999). The ability of the β-cells to compensate for the insulin resistance (the disposition index (DI)) was calculated as: (incremental AUC $ISR_{0\text{-}30}$ × incremental AUC $\text{glucose}_{0\text{-}30}{}^{-1}$) / (Matsuda index^{-1}) and (incremental AUC $ISR_{0\text{-}10}$ × incremental AUC $\text{glucose}_{0\text{-}10}{}^{-1}$) / (Matsuda index^{-1}) from OGTT and IVGTT data, respectively. The T2DM patients with the highest ($T2DM_{high}$) and lowest ($T2DM_{low}$) DI calculated from the IVGTT at the first examination were stratified into two equally sized sub-groups to investigate the role of the preoperative β-cell function for the outcome of RYGB. A P value <0.05 was considered significant. Statistical analysis was performed in SAS Enterprise 6.1 (SAS Institute Inc., Cary, NC, USA). Data are presented as means ± SEM.

Results

Weight, weight loss and BMI were similar in the two groups, but T2DM were ∼6 years older than OB (Table 1). Fasting plasma insulin concentrations were higher and fasting C-peptide similar in T2DM compared with OB. Fasting insulin decreased after the diet-induced weight loss, and fasting insulin and C-peptide were lower after surgery compared with before in both groups (Table 1). Fasting glucose concentrations were higher in T2DM compared with OB, and decreased after surgery in both

groups. Likewise, HbA1c was higher in T2DM compared with OB before and 4 months after surgery, and decreased after surgery only in T2DM (Table 1).

OGTT

The plasma glucose and insulin concentrations and the ISR during the OGTTs are shown in Fig. 1. Plasma glucose concentrations expressed as AUC were higher in T2DM compared with OB throughout the study (T2DM: A: 1155 ± 65, B: 1142 ± 83, C: 956 ± 93 and D: 927 ± 95 *vs.* OB: A: 768 ± 30, B: 757 ± 30, C: 708 ± 20 and D: 661 ± 20 mmol l^{-1} · 120 min, $P < 0.001$), and lower after surgery in both groups ($P < 0.003$). The plasma insulin concentrations during the OGTTs were lower in T2DM compared with OB (T2DM: A: 130 ± 27, B: 105 ± 19, C: 93 ± 18 and D: 85 ± 24 *vs.* OB: A: 177 ± 20, B: 181 ± 19, C: 175 ± 21 and D: 92 ± 13 pmol l^{-1} · 120 min · 10^2, $P = 0.02$) and lower 18 months after RYGB compared with the previous examinations in both groups ($P < 0.01$). The ISRs were lower in T2DM compared with OB (T2DM: A: 119 ± 24, B: 118 ± 20, C: 150 ± 19 and D: 151 ± 25 *vs.* OB: A: 172 ± 19, B: 199 ± 18, C: 237 ± 26 and D: 190 ± 21 pmol kg^{-1} · 120 min, $P = 0.02$) and did not change in response to either diet or RYGB in OB and T2DM. The β-cell glucose sensitivity was lower in T2DM compared with OB and increased after RYGB only in T2DM (Fig. 2). DI_{OGTT} and the Matsuda index were lower and HOMA-IR higher in T2DM compared with OB, and DIOGTT and the Matsuda index increased and HOMA-IR decreased postoperatively in T2DM and OB (Table 1).

GLP-1 and GIP concentrations in plasma during the OGTTs expressed as AUC are shown in Fig. 3. GLP-1 responses (T2DM: A: –131 ± 83, B: 195 ± 91, C: 933 ± 180 and D: 1219 ± 354 *vs.* OB: A: –160 ± 130, B: –91 ± 155, C: 1293 ± 270 and D: 1322 ± 327 pmol l^{-1} · 120 min) did not differ between T2DM and OB and markedly increased after surgery in both groups ($P < 0.001$). The plasma GIP concentrations (T2DM: A: 1036 ± 203, B: 1765 ± 211, C: 1107 ± 251 and D: 1123 ± 317 *vs.* OB: A: 973 ± 416, B: 1455 ± 135, C: 1471 ± 186 and D: 1026 ± 228 pmol l^{-1} · 120 min) were similar in the two groups and did not change after surgery.

IVGTT

The plasma concentrations of glucose and insulin and the ISR during the IVGTTs are shown in Fig. 4. The glucose concentrations were higher in T2DM compared with OB (T2DM: A: 528 ± 24, B: 510 ± 18, C: 483 ± 19 and D: 485 ± 20 *vs.* OB: A: 430 ± 11, B: 438 ± 12, C: 450 ± 11 and D: 452 ± 10 mmol l^{-1} · 40 min, $P < 0.001$), and did not change during the study in either group. The insulin concentrations were lower in T2DM compared with OB (T2DM: A: 56 ± 10, B: 58 ± 12, C: 37 ± 6 and D: 37 ± 7 *vs.* OB: A: 103 ± 14, B: 97 ± 13, C: 61 ± 11 and D: 40 ± 6 pmol l^{-1} · 40 min Here it should be 10 uplifted squared as for the OGTT result (Q9), $P < 0.007$), and decreased in both groups after RYGB ($P < 0.001$). The ISRs were lower in T2DM compared with OB (T2DM: A: 77 ± 12, B: 87 ± 10, C: 91 ± 14 and D: 98 ± 16 *vs.* OB: A: 141 ± 13, B: 158 ± 17, C: 148 ± 18 and D: 113 ± 11 mmol l^{-1} · 40 min) before and 4 months after RYGB ($P < 0.04$), but did not differ between groups 18 months after surgery. The ISR did not change in OB and tended to increase in T2DM 18 months after RYGB compared with baseline ($P = 0.06$). The DI_{IVGTT} was lower in T2DM than OB and increased after RYGB in both groups compared with baseline (Table 1).

The T2DM patients were then stratified into two groups according to DI_{IVGTT} (Table 2). There was no difference in age, weight, weight loss, BMI, fasting insulin, HOMA-IR or the Matsuda index between the two groups (Table 2). Duration of diabetes was shorter in $T2DM_{high}$ compared with $T2DM_{low}$ and DI_{IVGTT} and DI_{OGTT} were higher in $T2DM_{high}$ compared with $T2DM_{low}$. Fasting glucose and HbA1c were lower and fasting C-peptide higher in $T2DM_{high}$ compared with $T2DM_{low}$ (Table 2). First phase ISR during the IVGTT (Fig. 5) and β-cell glucose sensitivity during the OGTT (Fig. 2) were higher in $T2DM_{high}$ compared with $T2DM_{low}$ ($P < 0.001$), and both were restored by comparison with OB after surgery (Figs 2 and 5). First phase ISR (Fig. 5) ($P < 0.03$) and β-cell glucose sensitivity (Fig. 2) ($P = 0.01$) also increased in $T2DM_{low}$ after RYGB, but remained markedly impaired compared with $T2DM_{high}$ and OB 18 months after RYGB. There was no difference in postprandial GLP-1 concentrations in $T2DM_{high}$ compared with $T2DM_{low}$ (data not shown). The remission rate of type 2 diabetes was 57% and 0% 4 months after surgery and 71% and 38% 18 months after surgery in $T2DM_{high}$ and $T2DM_{low}$, respectively.

Discussion

In the present study morbidly obese subjects, with impaired or preserved β-cell function were followed during a massive weight loss. The major finding was the marked difference regarding the postoperative recovery of the first phase ISR during the IVGTT in the T2DM patients (Fig. 5). Thus, in $T2DM_{high}$ the ISR was markedly increased during the first 10 min of the test 4 months after surgery. The increased secretory capacity was maintained 18 months after RYGB and comparable to the response seen in OB (Fig. 5). In contrast, in the patients with the lowest initial β-cell function, $T2DM_{low}$, only minor

improvements in the capacity to secrete insulin were seen 4 and 18 months after surgery (Fig. 5).

Part of the difference in first phase ISR between the two T2DM groups is probably explained by the duration of diabetes (Table 2), but it should be noted that the groups did not differ with respect to baseline weight, BMI, age or insulin sensitivity (Table 2). Furthermore, the two groups had similar weight loss and postoperative postprandial GLP-1 concentrations. Regardless, the remission rate of type 2 diabetes after RYGB was twice as high in $T2DM_{high}$ compared with $T2DM_{low}$. The present prospective study is the first to stratify patients with type 2 diabetes with respect to their preoperative disposition index. The results show that preoperative β-cell function, assessed by an IVGTT, is a useful determinant for chance of remission of type 2 diabetes after RYGB, and suggest that early intervention may be important for the chance to experience remission. Previous studies have found fasting C-peptide to predict glycaemic control after RYGB (Aarts *et al.* 2013; Adams *et al.* 2013). In the present study C-peptide did not differ between OB and T2DM, but was higher in $T2DM_{high}$ compared with $T2DM_{low}$. Thus, the present data only partially agree with previous findings. This is likely explained by the markedly higher fasting glucose concentration in T2DM compared with OB stimulating fasting insulin secretion in the former group. Thus, our data underline that the fasting glucose concentration may be a confounding factor when using preoperative C-peptide concentrations for prediction of glycaemic control after RYGB. An earlier study by Nannipieri *et al.* (2011) showed marked difference in β-cell glucose sensitivity during an OGTT 1½ and 12 months after RYGB in patients with type 2 diabetes that experienced early, late or no remission of the diabetes, respectively. The findings in the present study are in line with this and show that the preoperative DI and first phase ISR may be equally important determinants for diabetes remission after RYGB.

The ISR AUC did not increase during the OGTT with surgery in OB and T2DM in the present study. However, the glucose dynamics changed after surgery with higher incremental ISR during the first 60 min after oral glucose administration, but lower ISR the following 60 min in both groups (Fig. 1). The result is in concordance with previous studies (Nannipieri *et al.* 2011; Jorgensen *et al.* 2012; Salinari *et al.* 2013) and a consequence of increased initial

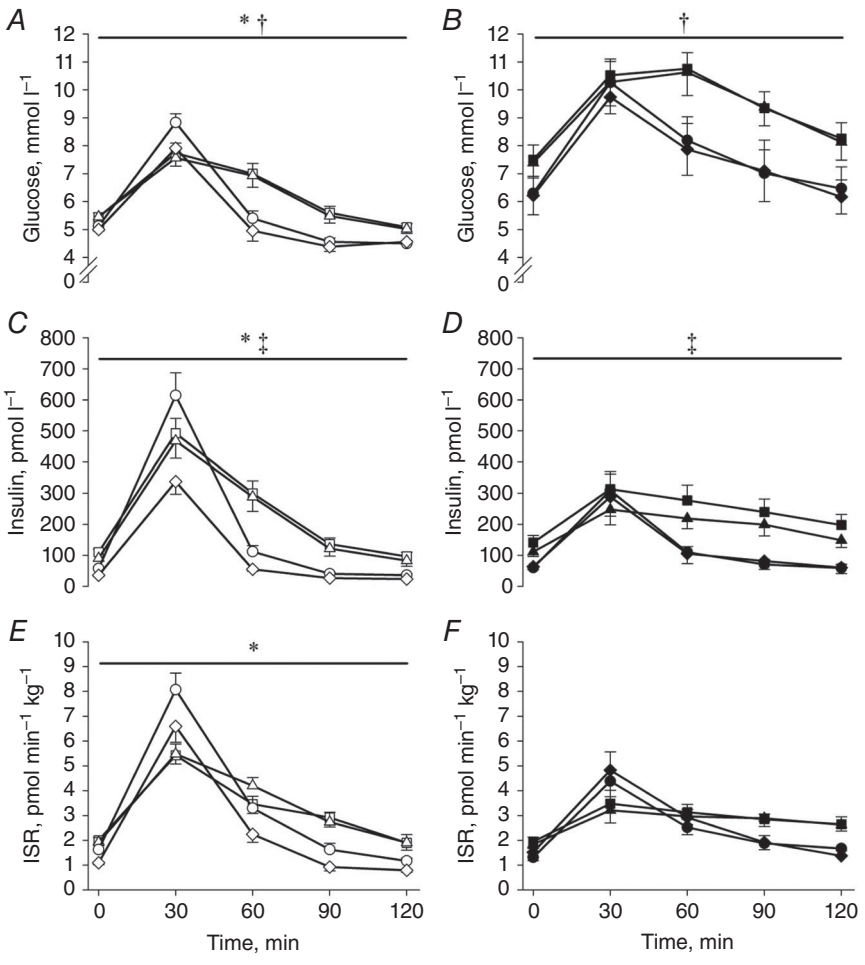

Figure 1. Plasma glucose (*A* and *B*) and insulin (*C* and *D*) concentrations and the ISR (*E* and *F*) during the OGTTs
Open symbols: OB; filled symbols: T2DM; squares: baseline (examination A); triangles: after a diet-induced weight loss (examination B); circles: 4 months after RYGB (examination C); diamonds: 18 months after RYGB (examination D). *Significantly different from T2DM; †significant difference between pre- and post-operative values; ‡Examination D significantly different from A, B and C. Data are means ± SEM.

glucose absorption and disposal with the surgery-induced change in gut anatomy (Jacobsen *et al.* 2012). The postprandial plasma GLP-1 concentration increased markedly with surgery in both groups and the postprandial GIP concentration did not change (Fig. 3). Neither of the incretin hormones differed between the groups. This is in line with the majority of previous studies investigating incretin release after RYGB when glucose or a mixed meal is administered orally (le Roux *et al.* 2007; Laferrere *et al.* 2007, 2008; Morinigo *et al.* 2006; Bose *et al.* 2010; Jorgensen *et al.* 2012; Salinari *et al.* 2013; Bojsen-Moller *et al.* 2014).

The glucose excursion was lower during the OGTT in both OB and T2DM after surgery and tended to be lower during the IVGTT in T2DM. This will affect the ISR during the tests and therefore the DI_{OGTT} is a better marker for β-cell function compared with the ISR in the present study. Stratifying the T2DM with respect to the DI_{OGTT} did not change the patient composition in $T2DM_{high}$ and $T2DM_{low}$. Thus, in the present study DI_{OGTT} and DI_{IVGTT} were equally good in predicting remission of diabetes after RYGB. The DI_{OGTT} increased in $T2DM_{high}$, $T2DM_{low}$ and OB after RYGB showing an improved ability in the β-cells to compensate for the prevailing insulin resistance (Table 1

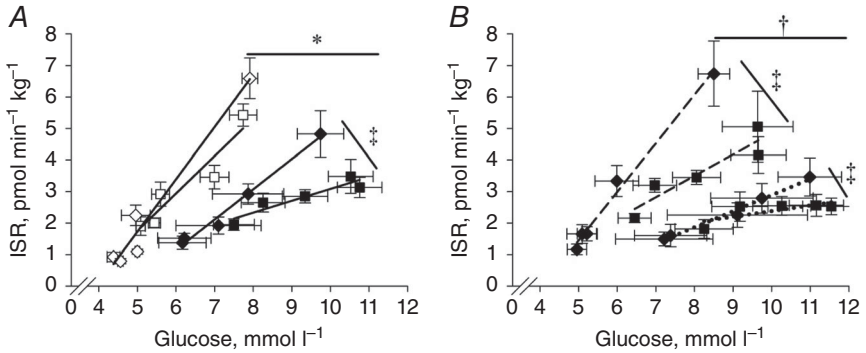

Figure 2. OGTT β-cell glucose sensitivity before and 18 months after RYGB
A, β-cell glucose sensitivity during the OGTTs before and 18 months after RYGB in OB and T2DM. *B*, β-cell glucose sensitivity during the OGTTs before and 18 months after RYGB in the T2DM with the initial highest or lowest β-cell function. The β-cell glucose sensitivity was calculated as the slope of curve obtained from all time points. Continuous lines and open symbols: OB; continuous lines and filled symbols: T2DM; squares: baseline (examination A); diamonds: 18 months after RYGB (examination D); dashed lines: $T2DM_{high}$; dotted lines: $T2DM_{low}$. *Significantly different from T2DM; †$T2DM_{high}$ significantly different from $T2DM_{low}$; ‡significant difference from baseline to 18 months after surgery. Data are means ± SEM.

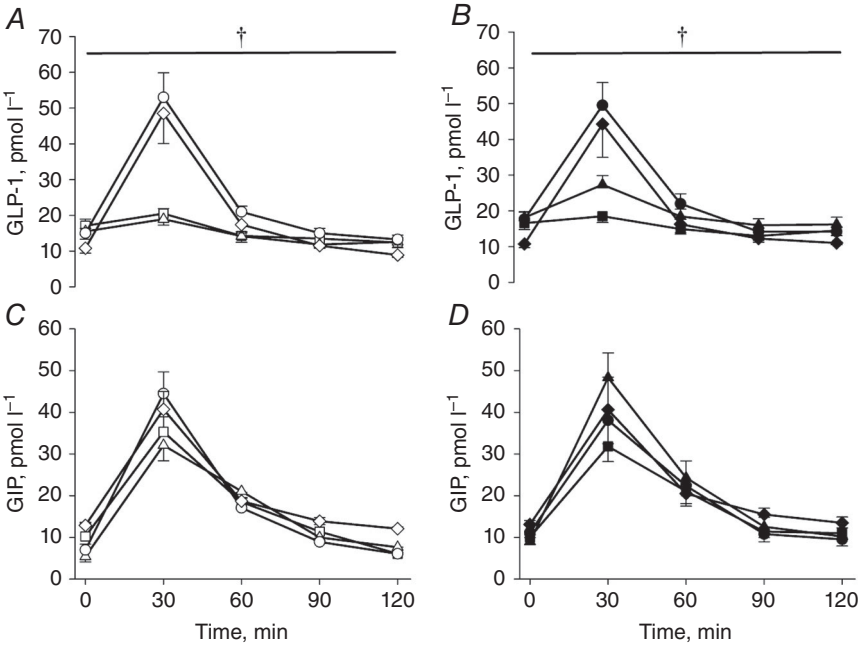

Figure 3. Plasma GLP-1 (*A* and *B*) and GIP (*C* and *D*) concentrations during the OGTTs
Open symbols: OB; filled symbols: T2DM; squares: baseline (examination A); triangles: after a diet-induced weight loss (examination B); circles: 4 months after RYGB (examination C); diamonds: 18 months after RYGB (examination D). †Significant difference between pre- and post-operative values. Data are means ± SEM.

and 2). In the T2DM, the increased DI_{OGTT} was the result of both increased insulin sensitivity and increased β-cell glucose sensitivity after RYGB (Table 2 and Fig. 2). The increased glucose sensitivity may be the result of both the markedly increased postoperative postprandial GLP-1 release which enhances glucose induced insulin secretion (the incretin effect) (Fig. 2) (Laferrere *et al.* 2007), and lower β-cell gluco- and lipotoxicity. Earlier studies by Salehi *et al.* (2011) and Jorgensen *et al.* (2013) have indicated that the increased postoperative GLP-1 release is important for the improved β-cell function in T2DM, but results from Jimenez *et al.* (2013) speak against this. Salinari *et al.* studied obese patients with and without type 2 diabetes before and 1 month after RYGB. The

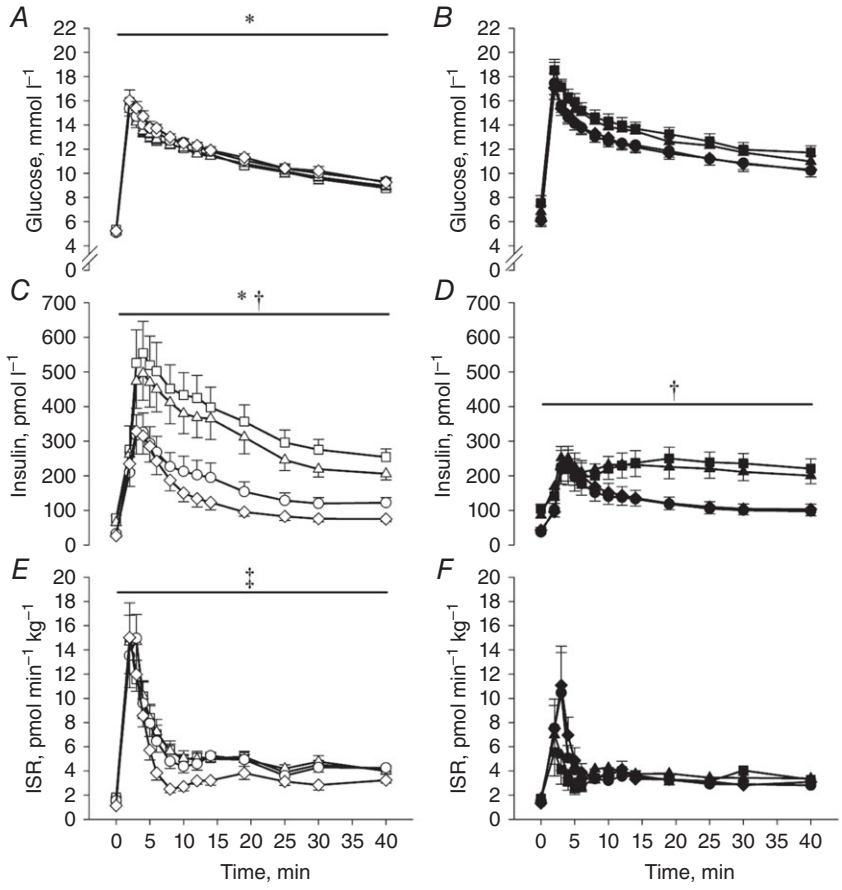

Figure 4. Glucose (*A* and *B*) and insulin (*C* and *D*) concentrations and the ISR (*E* and *F*) during the IVGTTs
Samples were drawn prior to glucose infusion and 2, 3, 4, 5, 6, 8, 10, 14, 19, 25, 30 and 40 min after. Open symbols: OB; filled symbols: T2DM; squares: baseline (examination A); triangles: after a diet-induced weight loss (examination B); circles: 4 months after RYGB (examination C); diamonds: 18 months after RYGB (examination D). *Significantly different from T2DM; †significant difference between pre- and post-operative values; ‡significantly different from T2DM at examination A, B and C. Data are means ± SEM.

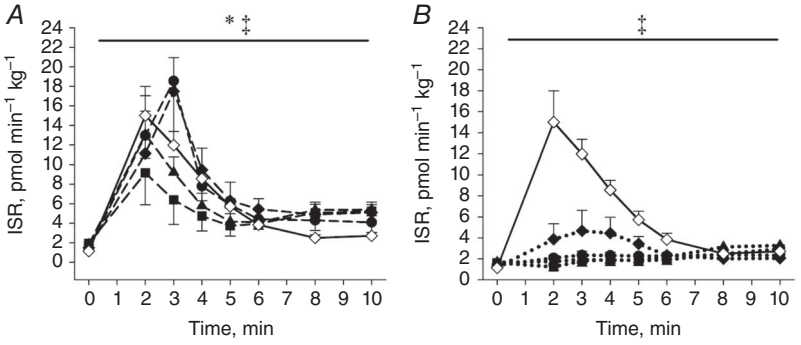

Figure 5. First phase ISR during the IVGTTs in OB and the T2DM with the initial highest (*A*) or lowest (*B*) β-cell function
OB examination D is added to the figures as a normal reference of the ISR. Open symbols: OB; filled symbols: T2DM; squares: baseline (examination A); triangles: after a diet-induced weight loss (examination B); circles: 4 months after RYGB (examination C); diamonds: 18 months after RYGB (examination D); dashed lines: $T2DM_{high}$; dotted lines: $T2DM_{low}$. *$T2DM_{high}$ significantly different from $T2DM_{low}$; ‡Examination C and D significantly different from A. Data are means ± SEM.

Table 2. Characteristics in the T2DM with the initial highest ($T2DM_{high}$) or lowest ($T2DM_{low}$) β-cell function

	$T2DM_{high}$				$T2DM_{low}$				Statistics		
	A	B	C	D	A	B	C	D	Group	Time	G x T
Sex (M/F)	4/3				2/6						
Age (years)	39 ± 2				44 ± 2				0.13		
Weight (kg)	128 ± 9	124 ± 10†	106 ± 7†	97 ± 11†	119 ± 6	116 ± 5†	92 ± 3†	84 ± 5†	0.18	< 0.001	0.99
Weight loss (%)		5 ± 1	21 ± 2†	28 ± 3†		5 ± 1	23 ± 1†	30 ± 3†	0.47	< 0.001	0.73
BMI (kg m^{-2})	41 ± 1	40 ± 2†	33 ± 1†	30 ± 2†	42 ± 2	41 ± 2†	33 ± 1†	30 ± 1†	0.97	< 0.001	0.86
Fasting insulin (pmol l^{-1})	100 ± 17	98 ± 10	46 ± 10‡	50 ± 5‡	121 ± 21	102 ± 13	48 ± 11‡	43 ± 13‡	0.78	< 0.001	0.47
Fasting C-peptide (pmol l^{-1})	777 ± 60	799 ± 59	522 ± 59‡	509 ± 21‡	643 ± 63	654 ± 62	464 ± 42‡	389 ± 56‡	0.02	< 0.001	0.74
Fasting glucose (mmol l^{-1})	6.6 ± 0.5	6.1 ± 0.3	5.3 ± 0.3‖	5.2 ± 0.1‡	8.9 ± 0.8	8.6 ± 0.7	7.4 ± 0.7‖	6.4 ± 0.3‡	< 0.001	0.003	0.70
HbA1c (mmol mol^{-1})	48 ± 3	41 ± 1†	38 ± 2‡	34 ± 2‡	63 ± 6	55 ± 5†	46 ± 4‡	47 ± 3‡	0.02	< 0.001	0.79
Matsuda index (a.u.)	1.5 ± 0.2	1.8 ± 0.2	4.2 ± 0.7‡	4.4 ± 0.7‡	1.7 ± 0.4	1.9 ± 0.3	4.3 ± 0.9‡	5.9 ± 1.9‡	0.68	< 0.001	0.84
HOMA-IR (a.u.)	2.1 ± 0.3	1.9 ± 0.2	0.9 ± 0.2‡	0.9 ± 0.1‡	2.4 ± 0.4	2.0 ± 0.2	1.0 ± 0.2‡	1.0 ± 0.2‡	0.50	< 0.001	0.58
DI_{OGTT} (a.u.)	1.2 ± 0.4	1.6 ± 0.3	3.5 ± 0.9‡	3.4 ± 1.1‡	0.4 ± 0.1	0.4 ± 0.1	1.0 ± 0.2‡	1.8 ± 1.0‡	< 0.001	< 0.001	0.53
DI_{IVGTT} (a.u.)	0.6 ± 0.2	1.0 ± 0.2	3.0 ± 0.5‡	3.4 ± 0.9‡	0.1 ± 0.1	0.1 ± 0.1	0.6 ± 0.3‡	1.9 ± 1.1‡	0.002	< 0.001	0.14
Diabetes (HbA1c > 42.1 mmol mol^{-1}, fasting glucose > 5.6 mmol l^{-1} or medication)	7	6	3	2	8	8	8	5			
Time since diagnosis (yrs)	1.5 ± 0.5				8.9 ± 2.4				0.01		
Medication (no. of patients)											
Antihypertensive	3	3	2	2	4	3	2	2			
Statins	1	1	1	1	1	1	1	1			
Metformin	1	1	0	0	6	6	1	1			
Insulin	1	1	0	0	3	3	0	0			
GLP-1 analog	2	2	0	0	2	2	0	0			
DPP-4 inhibitor	0	0	0	0	1	1	0	0			

HbA1c: glycosylated haemoglobin, type A1c; DI_{OGTT}: disposition index calculated from the OGTT; DI_{IVGTT}: disposition index calculated from the IVGTT; HOMA-IR: homeostatic model assessment of insulin resistance. †significantly different from previous examinations; ‡significantly different from pre-operative values; ‖significantly different from A. Data are means ± SEM.

authors found a minor, but significant, increase in first phase insulin ISR in T2DM after surgery, and a marked increase in the ISR during the OGTT (Salinari *et al.* 2013). Therefore, they suggested that the marked increase in post-prandial GLP-1 could be the trigger for increased ISR after RYGB (Salinari *et al.* 2013). In the present study the postoperative ISR was markedly increased in some, but not all, T2DM during the initial 10 min of the IVGTT (Figs 4 and 5). Thus, the difference between the two studies may be explained by the great preoperative variation in β-cell function in T2DM, as shown in the present study (Fig. 5), together with the low number of participants in the study by Salinari *et al.* (7 in each group). Recently Dutia *et al.* (2014) showed postoperative increased ISR during a 50 g OGTT, but not during an iso-glycaemic intravenous glucose infusion in 16 patients with type 2 diabetes. The authors therefore concluded that limited recovery of the β-cell function was seen after RYGB. Differences in the experimental designs may account for part of the different results between Dutia *et al.* and the present study. Thus, during an IVGTT the glucose concentration is markedly higher compared with an iso-glycaemic glucose infusion. Furthermore, the glucose concentration during an IVGTT and OGTT is not matched, and therefore cannot be used to calculate the incretin effect. Finally, time since diagnosis of type 2 diabetes was shorter in the present study ($T2DM_{high}$) compared with Dutia *et al.* Thus, the ability to regain β-cell function may be higher in the patients in the present study.

To ensure minimal discomfort for the patients after the RYGB a stimulus of 25 g of glucose was used both orally and intravenously. This may be seen as a limitation in the present study, because it will lead to a lower incretin effect during the OGTT. Thus, possible differences between the groups or after RYGB may be harder to identify. However, a robust postoperative increase in GLP-1 and GIP release was seen. Furthermore, dumping was avoided which otherwise could have resulted in exclusion of the patients who experienced this. After surgery patients spend ∼4 min consuming the glucose solution for the OGTT to avoid dumping symptoms. Regardless, postoperative glucose uptake was faster, seen as a steeper glucose concentration curve during the first 30 min of the OGTT, as a result of the changed gut anatomy (Fig. 1). The division of T2DM into $T2DM_{high}$ and $T2DM_{low}$ was done retrospectively. Since duration of diabetes, baseline disposition indexes and glycaemic control differed between the two groups, the influence of the individual parameters on diabetes

remission cannot be distinguished. However, the duration of diabetes and the β-cell function are likely to be linked, and glycaemic control markedly improved in both groups with weight loss diminishing any potential β-cell glucose toxicity.

The present study adds to our understanding of the restoration of the β-cell function after RYGB in several ways. First, a marked increase in β-cell function and normalization of first phase ISR are seen in some patients with short duration of type 2 diabetes when glucose is infused intravenously and no stimulation of the incretin hormones is present. Thus, in this group of patients factors apart from the increased incretin response seem to be important for the improved β-cell function after RYGB. Second, the total increase in β-cell function is lower, and the time needed to partly recover the function is longer in patients with low preoperative β-cell function. The results in the present study do not rule out an important role for GLP-1, but the data emphasize the importance of the preoperative β-cell function and disease duration, likely to be linked, for the chances of postoperative remission of type 2 diabetes.

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Additional information

Competing interests

The authors declare that they have no conflict of interest associated with this paper.

Author contributions

M.L. researched data and wrote manuscript. M.H., S.S. and S.D. researched data and reviewed the manuscript. M.S., A.K.F., K.B. recruited patients, performed the RYGB surgery and reviewed the manuscript. J.J.H. and J.W.H. analysed data and reviewed the manuscript. F.D. designed the study, researched data and reviewed/edited the manuscript.

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