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ARTICLE

Prospective evaluation of insulin and incretin dynamics in obese adults with and without diabetes for 2 years after Roux-en-Y gastric bypass

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Abstract

Aims/hypothesis In this prospective case–control study we tested the hypothesis that, while long-term improvements in insulin sensitivity (S_I) accompanying weight loss after Roux-en-Y gastric bypass (RYGB) would be similar in obese individuals with and without type 2 diabetes mellitus, stimulated-islet-cell insulin responses would differ, increasing (recovering) in those with diabetes but decreasing in those without. We investigated whether these changes would occur in conjunction with favourable alterations in meal-related gut hormone secretion and insulin processing.

Methods Forty participants with type 2 diabetes and 22 participants without diabetes from the Longitudinal Assessment of Bariatric Surgery (LABS-2) study were enrolled in a separate, longitudinal cohort (LABS-3 Diabetes) to examine the mechanisms of postsurgical diabetes improvement. Study procedures included measures of S_I, islet secretory response and gastrointestinal hormone secretion after both intravenous glucose (frequently-sampled IVGTT [FSIVGTT]) and a mixed meal (MM) prior to and up to 24 months after RYGB.

Results Postoperatively, weight loss and $S_{I\text{-}FSIVGTT}$ improvement was similar in both groups, whereas the acute insulin response to glucose (AIRglu) decreased in the non-diabetic participants and increased in the participants with type 2 diabetes. The resulting disposition indices ($DI_{FSIVGTT}$) increased by three- to ninefold in both groups. In contrast, during the MM, total insulin responsiveness did not significantly change in either group despite durable increases of up to eightfold in postprandial glucagon-like peptide 1 levels, and $S_{I\text{-}MM}$ and DI_{MM} increased only in the diabetes group. Peak postprandial glucagon levels increased in both groups.

Conclusions/interpretation For up to 2 years following RYGB, obese participants without diabetes showed improvements in DI that approach population norms. Those with type 2 diabetes recovered islet-cell insulin secretion response yet continued to

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Research in context

What is already known about this subject?

- Gastric bypass surgery reduces weight and improves glucose metabolism in obese individuals
- Mechanisms for both of these effects are thought to include enhanced secretion of key gut hormones

What is the key question?

- Over a 2 year period, how does gastric bypass change glucose and gut hormone levels and what are the corresponding changes in insulin sensitivity, insulin secretory capacity and disposition index in obese individuals with and without diabetes?

What are the new findings?

- Increases in postprandial glucagon-like peptide 1 (GLP-1) secretion (nearly eightfold vs baseline) and peak glucagon levels in both groups after gastric bypass are durable up to 2 years
- Gastric bypass improves disposition index in those without diabetes to nearly match population norms after 2 years, even though insulin secretion in response to i.v. glucose declines
- In individuals with diabetes, disposition indices and insulin secretion in response to i.v. glucose both improve after gastric bypass, but after 2 years still remain well below population norms

How might this impact on clinical practice in the foreseeable future?

- In order to maximise islet cell recovery, gastric bypass should be considered prior to onset of diabetes

manifest abnormal insulin processing, with DI values that remained well below population norms. These data suggest that, rather than waiting for lifestyle or medical failure, RYGB is ideally considered before, or as soon as possible after, onset of type 2 diabetes.

Trial registration ClinicalTrials.gov NCT00433810

Keywords Disposition index · Frequently-sampled intravenous glucose tolerance test · Gastric bypass · GIP · GLP-1 · Glucagon · Insulin secretion · Insulin sensitivity · Lipids · Meal test · Obesity · Proinsulin · Remission

Abbreviations

Φ_d	Dynamic beta cell responsivity
Φ_s	Static beta cell responsivity
AIRglu	Acute insulin response to glucose
DI	Disposition index
FSIVGTT	Frequently-sampled IVGTT
GIP	Gastric inhibitory polypeptide
GLP-1	Glucagon-like peptide 1
HE	Hepatic insulin extraction
LABS	Longitudinal Assessment of Bariatric Surgery
MM	Mixed meal
RYGB	Roux-en-Y gastric bypass
S_G	Glucose effectiveness
S_I	Insulin sensitivity

Introduction

Bariatric/metabolic surgery has been shown to improve glycaemic control and often induces remission of type 2 diabetes in obese individuals [1–3]. Previous studies have consistently demonstrated improvements in insulin sensitivity proportional to the amount of weight loss following bariatric surgery [4–6]. Given the importance of declining islet-cell function in the pathogenesis of type 2 diabetes [7] and the prominent effects of Roux-en-Y gastric bypass (RYGB) on the secretion of gut hormones involved in islet-cell secretory responses, we designed a study to better understand the effect of RYGB on islet-cell function in response to both oral (mixed meal [MM]) and intravenous nutrient stimulation. Study times after surgery included an early point at which weight loss was still ongoing and a later visit when weight was at or near its nadir [8].

We hypothesised that, because of altered nutrient flow through the gastrointestinal tract after RYGB, changes in key gut hormones known to influence islet-cell insulin secretion (such as glucagon-like peptide 1 [GLP-1] and possibly gastric inhibitory polypeptide [GIP]) would occur early and be maintained long-term. In addition, we hypothesised that in individuals with and without type 2 diabetes, insulin sensitivity would improve with

postsurgical weight loss in both groups and that the proinsulin-to-insulin ratio would decrease, reflecting improved islet-cell insulin-processing efficiency. On the other hand, we hypothesised that the postsurgical stimulated-islet-cell secretory responses would differ. In non-diabetic individuals in whom hyperinsulinaemia compensates for insulin resistance allowing maintenance of normal glucose levels at baseline, insulin secretion would be reduced after surgery, reflecting decreased demand accompanying improved insulin sensitivity. In contrast, in individuals with type 2 diabetes, in whom defective islet function manifests in baseline hyperglycaemia, post-RYGB stimulated insulin secretory capacity would recover (increase). If the latter is shown to be true, these data would not only provide important insights into mechanisms of diabetes remission and prevention after RYGB, but would also place this procedure among a handful of interventions shown to reverse the decline in beta cell function that accompanies onset and progression of type 2 diabetes [9].

Methods

The Longitudinal Assessment of Bariatric Surgery (LABS) study is a prospective, longitudinal cohort study with three phases: LABS-1, LABS-2 and LABS-3 [10]. LABS-1 is complete and reported 30 day postsurgical adverse outcomes in nearly 5000 participants [11]. LABS-2 is a cohort of 2458 participants and has a primary goal of evaluating long-term efficacy of bariatric surgery [8]. The LABS-3 Diabetes substudy comprised a subcohort from the LABS-2 study recruited specifically to better understand the physiological mechanisms of glucose metabolism improvement following RYGB.

Participants and study visits Candidates were approached for inclusion if they were scheduled for RYGB at a participating LABS-2 site at the University of Pittsburgh, University of Washington or Oregon Health & Science University (ESM Fig. 1). Individuals with diabetes were included if they were documented to have a fasting plasma glucose ≥7.0 mmol/l and ≤10 mmol/l or HbA_{1c} ≥48 mmol/mol (6.5%) and ≤69 mmol/mol (8.5%) and were treated with lifestyle interventions alone or metformin and/or sulfonylurea. Exclusion criteria included type 1 diabetes, creatinine >150 μmol/l, treatment with insulin or other non-metformin/non-sulfonylurea diabetes medications, treatment with weight-loss medications and individuals unlikely or unwilling to comply with follow-up visits. Participants on metformin, without a pre-treatment glucose or HbA_{1c} measurement but meeting criteria for diabetes, were assumed to be on this therapy for diabetes prevention, weight loss or polycystic ovarian syndrome, and were excluded. Control participants (those without diabetes) were included if their fasting plasma glucose was <7.0 mmol/l and/or their HbA_{1c} was <48 mmol/mol (6.5%) and they were not taking any diabetes medications. They were matched to participants with diabetes based on age, sex and pre-surgical BMI. All studies were approved by the investigational review boards at each site and consent was obtained from each participant before enrolment.

In the week before each research study visit, participants met with a registered dietitian to receive instruction regarding a standardised diet consisting of ~30% total energy from fat, ~10–15% from protein and ~55–60% from carbohydrates. During this time, participants with diabetes also stopped their diabetes medications and self-monitored their capillary blood glucose levels at home. All other usual medications for comorbid conditions (i.e. hypertension, gastroesophageal reflux and hyperlipidaemia) were continued, as was treatment for obstructive sleep apnoea.

At the end of this pre-study week, participants presented to the clinical research centres at their respective institutions following an overnight fast on each of 2 days, scheduled not more than a week apart. On one day, fasting blood samples were drawn for lipids and proinsulin levels after which participants were given an MM (BOOST Plus, Nestlé Health Science, Epalinges, Switzerland; 1506 kJ (360 kcal), 45 g carbohydrate, 14 g fat, 14 g protein). Blood samples were obtained for glucose, insulin, C-peptide, glucagon, GLP-1 and GIP 15 min before and 0, 10, 20, 30, 60, 90, 120, 150, 180 and 240 min after meal consumption. On the other day, they underwent an insulin-modified frequently-sampled IVGTT (FSIVGTT) [12].

Following these baseline studies, participants underwent identical procedures as described above at 6 and 24 months after RYGB.

Biochemical analysis Determination of glucose was performed by the hexokinase method using Roche reagents (Roche Diagnostics, Indianapolis, IN, USA). Levels of insulin and C-peptide were measured by a two-site enzymometric assay using Tosoh reagents on a Tosoh 2000 autoanalyzer (Tosoh Corp., Tokyo, Japan). Proinsulin levels were determined by radioimmunoassay using a Millipore kit (MilliporeSigma, Burlington, MA, USA). All lipid analyses were performed at the Northwest Lipid Metabolism and Diabetes Research laboratory, University of Washington, Seattle, WA, USA.

Total GLP-1, total GIP, total adiponectin and glucagon were measured by the Oregon Health & Science University Oregon Clinical and Translational Research Laboratory, Portland, OR, USA. To determine total GLP-1 and total GIP, blood was collected into EDTA vacutainers (prepared with 500 KU aprotinin and 10 μl dipeptidyl-peptidase-4 inhibitor per ml of whole blood) on ice. To determine adiponectin, blood was collected into EDTA vacutainers (prepared with 500 KU aprotinin/ml whole blood) on ice. These three

analytes were measured using single-plex immunoassays from Meso Scale Discovery/Sector Imager (Gaithersburg, MD, USA). Glucagon was measured in blood collected in heparin vacutainers on ice, prepared with 500 KU aprotinin/ml whole blood, using an RIA from EMD Millipore (Billerica, MA, USA). The specificity of the glucagon assay was established by testing cross-reactivity with several gut hormones: oxyntomodulin (0.02%), 7-37 GLP-1 (none), 7-36 GLP-1 (<0.01%) and 1-37 GLP-1 (none).

Definition of diabetes and diabetes remission Diabetes remission included both partial and complete remission, according to the American Diabetes Association Consensus Group recommendation [13], as HbA_{1c} <48 mmol/mol (6.5%) (or fasting glucose ≤6.9 mmol/l if HbA_{1c} was not available) and the absence of concurrent pharmacological therapy for diabetes.

Modelling for insulin secretory response and insulin sensitivity Insulin sensitivity (S_I), beta cell responsivity to glucose (Φ; measured as Φ total, Φ basal, Φ dynamic and Φ static) and hepatic insulin extraction (HE basal and HE total) were determined during the MM as previously described [14]. Disposition index (DI) during the MM was derived from the product of S_I and Φ total. Variables of sensitivity to insulin and secretion response during the FSIVGTT, including S_I, glucose effectiveness (S_G) and acute insulin response to glucose (AIRglu), were modelled as previously described [15]. The DI during the FSIVGTT was derived from the product of S_I and AIRglu.

Statistical analysis Forty participants with type 2 diabetes and 20 without diabetes (60 in total) were estimated to provide an effective sample size for detecting modest-to-large effects on insulin sensitivity and stimulated-islet-cell secretion for within-person analyses and large-to-very-large effect sizes for between-group analyses based on prior studies [16, 17]. For continuous measures, participants in the diabetes vs no-diabetes groups were compared based on a Wilcoxon Rank Sum test to assess statistical significance of differences, unless normally distributed, in which case paired *t* tests were performed. For categorical measures, the frequency and percentage of each category was reported, and a Pearson χ^2 test was used for statistical significance. For tables with small cell frequencies, Fisher's exact test was used. Measures of insulin secretion and sensitivity from the FSIVGTT and MM over time were modelled using generalised linear models which included a heterogeneous autoregressive working correlation matrix to account for the correlation between successive measures. The model assumed a γ distribution for the measures to account for the highly skewed nature of the data. The mean measures at 6 months and 24 months were compared with baseline measures using a Wald *t* test. Missing values were treated as random occurrences. The generalised linear models used here utilised likelihood-based inference under which estimates are unbiased when data are missing completely at random.

Results

Sixty-two participants (40 with type 2 diabetes and 22 without diabetes) were enrolled and did not differ by group with respect to percentages of women and race, or by baseline age, BMI, percentage body fat or presence of obstructive sleep apnoea (Table 1). In participants with diabetes in whom the information was obtained ($n = 24$), the median duration of diabetes was 3.0 years. At baseline, $HbA_{1c,}$ fasting glucose, proinsulin and proinsulin:insulin ratios were all higher in the participants with diabetes than in the non-diabetic participants, but fasting insulin, C-peptide and total adiponectin levels were no different (Table 2).

Median weight loss was similar in both groups at 6 months (24% vs 26% in participants with vs without diabetes, $p = 0.27$) and 24 months (29% vs 32% in participants with vs without diabetes, $p = 0.57$) (Fig. 1). Accompanying this weight loss, fasting glucose and insulin levels were lower than baseline at each follow-up visit in both groups (Fig. 2 and Table 2). Compared with baseline, two years after surgery HbA_{1c} levels significantly decreased to 31 mmol/mol (5.0%) in non-diabetic participants and 33 mmol/mol (5.2%) in participants with type 2 diabetes (Table 2), remaining marginally higher in the diabetes group ($p = 0.017$). Compared with baseline, at both follow-up visits the time to peak glucose and insulin levels during the MM shifted to an earlier time point (30 vs 60–90 min) in each group ($p < 0.001$, Fig. 2). On the other hand, the peak postprandial glucose level increased compared with baseline in the non-diabetic participants ($p < 0.001$) but not in those with diabetes (Fig. 2 and Table 3). Similarly, peak postprandial insulin concentrations at each follow-up time point were higher than at baseline in both groups (Fig. 2 and Table 3). Despite these high early postprandial levels for both glucose and insulin following a meal, AUC levels had decreased by the visit at 6 months and remained lower than baseline at 24 months (Table 3).

Fasting levels of GIP were not different and fasting GLP-1 levels were lower after surgery compared with baseline in both groups (although the difference in GLP-1 did not reach statistical significance in the non-diabetes group) (Table 3). However, the postprandial increases in levels of these hormones following an MM mirrored those of glucose and insulin in both groups (Fig. 3). Peak GIP shifted 30 min earlier and AUC GIP was lower at 6 and 24 months compared with baseline (Fig. 3 and Table 3). Peak GLP-1 levels increased seven- to eightfold, and AUC levels were significantly increased in both groups at 6 and 24 months after surgery compared with baseline (Fig. 3 and Table 3). Also in both groups, fasting glucagon levels decreased after surgery but peak levels following the MM increased and the increase in AUC approached statistical significance at both 6 months and 24 months after surgery (Fig. 3 and Table 3).

Glucose metabolism variables following an MM Using a standardised MM to derive meal-related variables of insulin

Table 1 Baseline characteristics of participants with and without type 2 diabetes

Variable	Diabetes ($N = 40$)	Without diabetes ($N = 22$)	p value
Female sex, %	75	77	0.84
Race, %			0.94
White	95	95	
Other	5	5	
Age, years	52 (47, 57)	52 (45, 54)	0.88
BMI, kg/m^2	47.9 (43.1, 54.8)	45.7 (43.6, 50.7)	0.57
Duration of diabetes, years[a]	3.0 (1.75, 5.5)	–	
Diabetes treatment, *n* (%)	29 (72.5)	–	
No medications (diet alone), *n* (%)	11 (27.5)	–	
Metformin, *n* (%)	21 (52.5)	–	
Sulfonylurea, *n* (%)	10 (25)	–	
Obstructive sleep apnoea, *n* (%)	31 (77.5)	20 (90.9)	0.30

Data expressed as %, *n* (%) or median (25th percentile, 75th percentile)

[a] Data are for 24 participants

Table 2 Fasting metabolic variables prior to and after RYGB in participants with and without type 2 diabetes

Variable	Baseline		6 Months			24 Months		
	n	Mean (95% CI)	*n*	Mean (95% CI)	*p* value (vs baseline)	*n*	Mean (95% CI)	*p value* (vs baseline)
Fasting glucose, mmol/l								
With diabetes	39	7.30 (6.73, 7.87)***	38	5.21 (4.93, 5.49)**	<0.001	35	5.24 (5.03, 5.45)	<0.001
Without diabetes	21	5.26 (5.09, 5.43)	22	4.74 (4.58, 4.9)	<0.001	17	5.00 (4.84, 5.15)	0.011
Fasting insulin, pmol/l								
With diabetes	39	129.7 (102.8, 156.5)	37	47.7 (36.9, 58.6)	<0.001	35	41.5 (32.4, 50.6)	<0.001
Without diabetes	21	130.5 (91.4, 169.5)	22	37.2 (30.4, 44)	<0.001	17	36.9 (29.1, 44.7)	<0.001
HbA_{1c}, mmol/mol								
With diabetes	36	46 (43–49)***				35	33 (32, 36)*	<0.001
Without diabetes	22	34 (33, 36)				15	31 (30, 32)	<0.001
HbA_{1c}, %	36					35		
With diabetes	36	6.4 (6.1, 6.6)***				35	5.2 (5.1, 5.4)*	<0.001
Without diabetes	22	5.3 (5.2, 5.4)				15	5.0 (4.9, 5.1)	<0.001
C-peptide, nmol/l								
With diabetes	39	1.3 (1.1, 1.5)	38	0.70 (0.60, 0.83)	<0.001	35	0.70 (0.57–0.80)	<0.001
Without diabetes	21	1.1 (0.90, 1.4)	22	0.57 (0.50, 0.67)	<0.001	17	0.67 (0.57, 0.77)	<0.001
Proinsulin, pmol/l								
With diabetes	39	40 (26, 54)**	36	12 (8.8, 15)**	<0.001	35	8.9 (6.0, 12)*	<0.001
Without diabetes	21	18 (14, 21)	22	6.5 (5.6, 7.4)	<0.001	17	5.2 (4.7, 5.8)	<0.001
Proinsulin:insulin ratio								
With diabetes	39	2.2 (1.8, 2.7)***	36	1.8 (1.6, 2.1)**	0.05	35	1.8 (1.2, 2.3)*	0.13
Without diabetes	21	1.1 (0.9, 1.4)	22	1.3 (1.1, 1.5)	0.17	17	1.1 (0.91, 1.4)	0.89
Adiponectin, μg/ml								
With diabetes	40	7.35 (6.17, 8.53)	37	11.6 (9.9, 13.3)	<0.001	35	14.7 (12.0, 17.5)	<0.001
Without diabetes	21	8.38 (7.08, 9.67)	22	11.7 (9.06, 14.3)	0.001	17	14.6 (11.6, 17.6)	<0.001

Estimates are based on Wald *t* test from generalised linear model

*$p < 0.05$, **$p < 0.01$ and ***$p < 0.001$ vs without diabetes

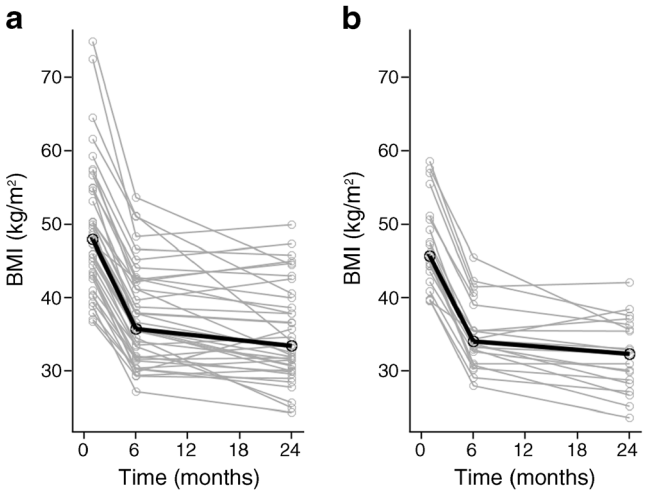

Fig. 1 Median (bold black line) and individual (grey lines) BMI at baseline and at 6 and 24 months after RYGB in 40 participants with type 2 diabetes (**a**) and 22 participants without diabetes (**b**). Median total weight loss after 6 months was 24% in participants with type 2 diabetes and 26% in participants without diabetes ($p = 0.27$), and after 24 months was 29% in participants with type 2 diabetes and 32% in participants without diabetes ($p = 0.57$)

secretion and sensitivity [14], participants with and without type 2 diabetes exhibited reduced basal (fasting) beta cell responsivity (Φb) and slight increases in basal HE (Table 4) ($p < 0.001$ for all comparisons) at 6 and 24 months after RYGB. During the follow-up visit at 24 months, despite an overall 32% reduction in the amount of secreted insulin per unit increase of glucose during the dynamic phase of the meal, or dynamic beta cell responsivity (Φ_d), Φ_d remained significantly higher in the non-diabetic participants than in those with diabetes, in whom Φ_d did not significantly change after surgery (Table 4). Static beta cell responsivity (Φ_s, the amount of insulin secreted in response to glucose during the static phase compared with basal state) and total Φ (the overall beta cell responsivity derived from Φ_d and Φ_s) were higher in the participants without diabetes than in those with type 2 diabetes at each study visit, but did not significantly change in either group as a result of the surgery and accompanying weight loss (Table 4). Conversely, the total HE during the meal was greater in participants with diabetes than in those without, both at baseline and during follow-up, but did not significantly change in either group following surgery. Insulin sensitivity derived during the meal test ($S_{I\text{-}MM}$) improved 6 months after surgery in both groups and continued to increase in participants with diabetes thereafter. However, the increase was no longer significantly different from baseline in participants without diabetes after 24 months, despite continued weight loss (Table 4). Despite this increase in $S_{I\text{-}MM}$, insulin sensitivity remained lower in participants with diabetes than in those without at all three study visits. The meal-derived disposition index (DI_{MM},) representing insulin secretion response to a given level of insulin sensitivity (calculated as the product of total Φ and $S_{I\text{-}MM}$), was lower in participants with type 2 diabetes than in those without diabetes, at each visit. In the diabetes group, DI_{MM} was higher 6 and 24 months after

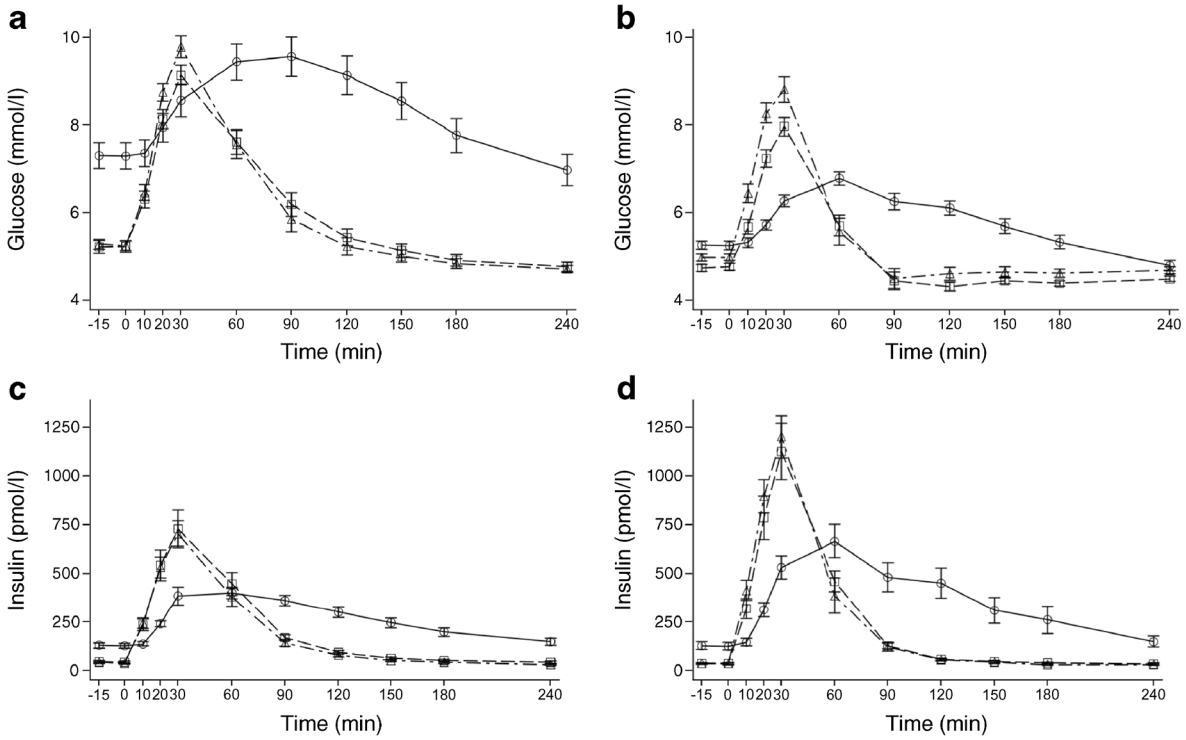

Fig. 2 Mean ± SEM for glucose (**a**, **b**) and insulin (**c**, **d**) levels during the MM in participants with (**a**, **c**) and without (**b**, **d**) type 2 diabetes at baseline (circles) and at 6 months (squares) and 24 months (triangles) after RYGB

Table 3 Baseline and postsurgical levels of glucose, insulin and gut hormones secreted following an MM prior to and after RYGB in participants with and without type 2 diabetes

Variable	Baseline		6 Months			24 Months		
	n	Mean (95% CI)	*n*	Mean (95% CI)	*p* value (vs baseline)	*n*	Mean (95% CI)	*p* value (vs baseline)
Peak glucose, mmol/l								
With diabetes	39	9.96 (9.14, 10.78)***	38	9.32 (8.89, 9.75)***	0.09	35	9.79 (9.32, 10.25)*	0.69
Without diabetes	21	6.88 (6.57, 7.18)	22	7.98 (7.56, 8.4)	<0.001	17	9.05 (8.62, 9.48)	<0.001
Glucose AUC, mmol (4 h) l^{-1}								
With diabetes	39	2130 (1942, 2319)***	38	1523 (1445, 1602)***	<0.001	35	1472 (1385, 1559)*	<0.001
Without diabetes	21	1448 (1382, 1514)	22	1278 (1234, 1321)	<0.001	17	1347 (1298, 1395)	0.022
Peak insulin, pmol/l								
With diabetes	39	491.9 (405.1, 578.7)**	38	807.5 (617, 997.9)	<0.001	35	771.4 (641.5, 901.4)***	<0.001
Without diabetes	21	778.3 (596.8, 959.7)	22	1137.4 (863.7, 1411.2)	0.003	17	1221 (1022.1, 1419.8)	<0.001
Insulin AUC, pmol (4 h) l^{-1}								
With diabetes	39	66,376 (57,212, 75,539)	38	51,305 (41,779, 60,832)	<0.001	35	44,929 (38,306, 51,552)	<0.001
Without diabetes	21	89,867 (66,916, 112,818)	22	57,628 (46,770, 68,487)	0.001	17	57,365 (46,776, 67,954)	0.006
Fasting GIP, pmol/l								
With diabetes	40	16.5 (13.3, 19.7)	38	13.5 (12, 15.1)	0.029	35	14.6 (12.9, 16.3)	0.17
Without diabetes	21	15.1 (12.3, 18)	22	12.5 (10.8, 14.2)	0.1	17	14.7 (12.9, 16.5)	0.78
Peak GIP, pmol/l								
With diabetes	40	140.4 (124, 156.9)	38	150.9 (131.1, 170.7)	0.29	35	159.4 (133.7, 185.1)	0.14
Without diabetes	21	129.2 (103.8, 154.6)	22	156.6 (130.3, 182.8)	0.036	17	135.1 (112.4, 157.9)	0.62
GIP AUC, pmol (4 h) l^{-1}								
With diabetes	40	16,167 (14,522, 17,813)	38	11,727 (10,355, 13,099)	<0.001	35	12,435 (10,544, 14,325)	<0.001
Without diabetes	21	15,879 (13,280, 18,478)	22	13,126 (11,146, 15,107)	0.004	17	12,048 (10,042, 14,055)	0.001
Fasting GLP-1, pmol/l								
With diabetes	40	4.3 (3.5, 5.2)	37	3.5 (2.9, 4.0)	0.04	35	3.3 (2.8, 3.9)	0.011
Without diabetes	20	4.4 (3.3, 5.4)	21	2.7 (2.1, 3.3)	<0.001	17	3.5 (2.7, 4.3)	0.05
Peak GLP-1, pmol/l								
With diabetes	40	9.7 (7.4, 11.9)	38	68.5 (59.2, 77.7)	<0.001	35	66.9 (58.3, 75.5)	<0.001
Without diabetes	21	12.2 (3.1, 21.3)	22	66.2 (49.7, 82.6)	<0.001	17	69.2 (56.5, 82.0)	<0.001
GLP-1 AUC, pmol/l								
With diabetes	40	1445 (1243, 1647)	38	4441 (3971, 4912)	<0.001	35	4067 (3629, 4505)	<0.001
Without diabetes	21	1399 (1068, 1730)	22	4194 (3435, 4953)	<0.001	17	3910 (3282, 4538)	<0.001
Fasting glucagon, ng/l								
With diabetes	40	78.5 (71.6, 85.4)	38	66.1 (59.9, 72.4)	<0.001	35	66.8 (61.5, 72.1)	<0.001
Without diabetes	21	85 (72, 97.9)	22	70 (60.8, 79.2)	<0.001	17	68.6 (59, 78.2)	<0.001
Peak glucagon, ng/l								
With diabetes	40	102.2 (91.9, 112.5)	38	113.3 (106.5, 120)	0.045	35	112.3 (105.4, 119.2)	0.05
Without diabetes	21	99.2 (84.7, 113.8)	22	105.9 (94.9, 116.8)	0.17	17	109.9 (97.5, 122.3)	0.05
Glucagon AUC, ng (4 h) l^{-1}								
With diabetes	40	20,490 (18,782, 22,198)	38	21,880 (20,834, 22,925)	0.06	35	21,526 (20,124, 22,928)	0.19
Without diabetes	21	21,356 (18,312, 24,401)	22	22,023 (19,867, 24,179)	0.44	17	23,083 (20,385, 25,780)	0.14

Estimates are based on Wald *t* test from generalised linear model

*$p < 0.05$, **$p < 0.01$ and ***$p < 0.001$ vs without diabetes

surgery compared with baseline, whereas in the non-diabetes group it remained high and unchanged from baseline throughout (Table 4 and Fig. 4).

Glucose metabolism variables derived from FSIVGTTs Derived measures of insulin secretion and sensitivity during the FSIVGTT (Table 5) showed that the acute insulin response to

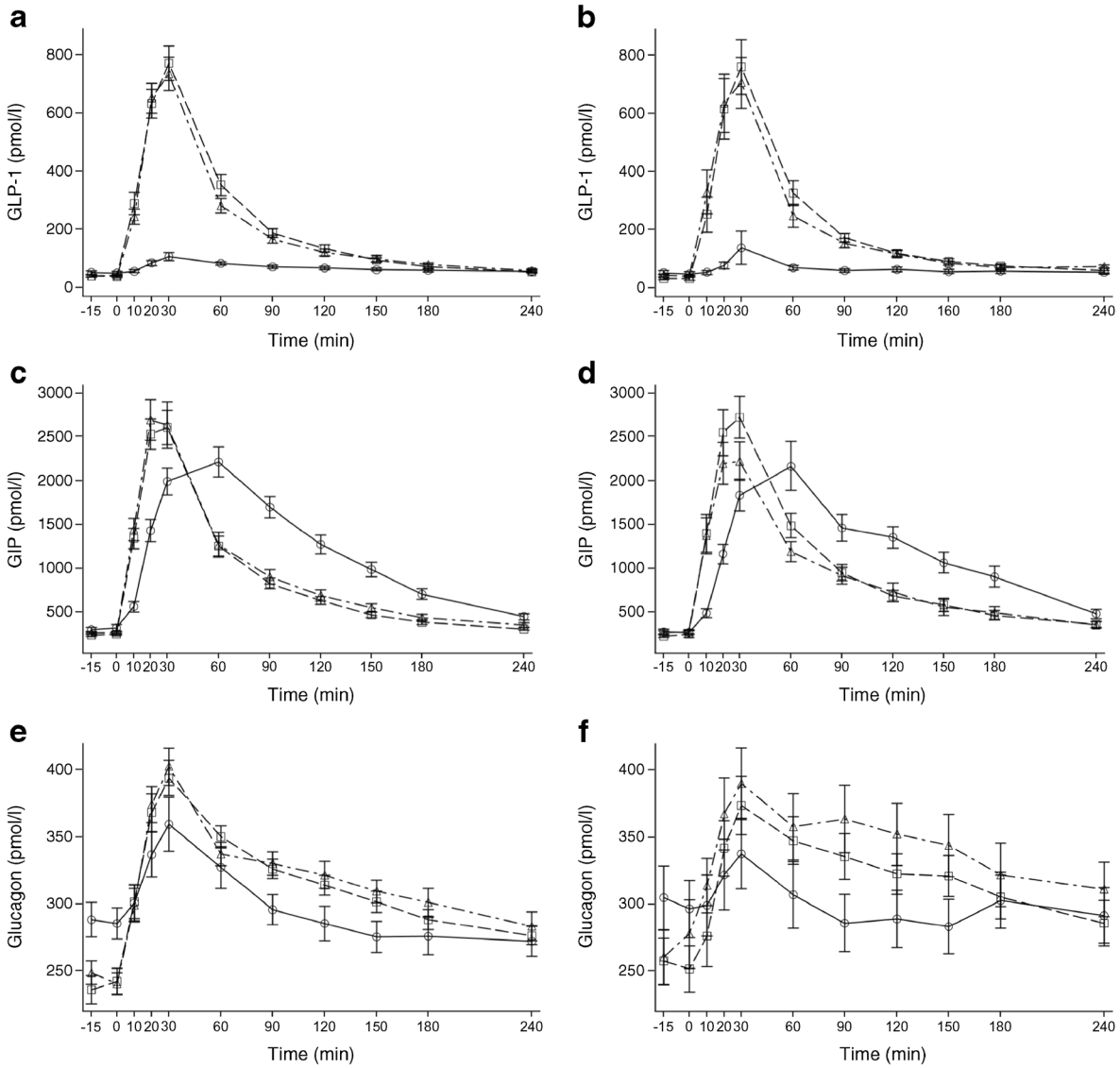

Fig. 3 Mean ± SEM for GLP-1 (**a**, **b**), GIP (**c**, **d**) and glucagon (**e**, **f**) during the MM in participants with (**a**, **c**, **e**) and without (**b**, **d**, **f**) type 2 diabetes at baseline (circles) and at 6 months (squares) and 24 months (triangles) after RYGB

intravenously administered glucose, AIRglu, significantly increased in the participants with type 2 diabetes and decreased in the non-diabetic participants. Insulin sensitivity ($S_{I\text{-}FSIVGTT}$) was greater at baseline in participants without diabetes than in those with diabetes, and both groups experienced significant improvements in insulin sensitivity such that by 24 months they were no longer significantly different from one another. Despite divergent changes in AIRglu, the FSIVGTT-derived disposition index ($DI_{FSIVGTT}$) increased roughly ninefold in participants with diabetes and 2.5-fold in non-diabetic participants by 24 months after surgery compared with baseline (Table 5 and Fig. 4). Glucose effectiveness (S_G) did not differ between the groups and was not affected by surgery or weight loss.

Diabetes remission and characteristics of participants with diabetes that persisted or recurred after surgery None of the non-diabetic participants developed diabetes during the 24 months of follow-up. Of the 40 participants with diabetes enrolled at baseline, 34 had data to determine diabetes status at 24 months. Of these, three were classified as having diabetes at 24 months (91% remission rate). Two of these three participants were taking diabetes medication at 6 months, whereas the third was not taking any diabetes medications at either of those time points.

Discussion

The current study was undertaken to compare 2 year changes in insulin sensitivity and secretory responses, and levels of gastrointestinal hormones, measured during oral (MM) and intravenous (FSIVGTT) challenges in obese participants with and without diabetes following RYGB.

Table 4 Variables of insulin sensitivity and secretion derived from the MM test prior to and after RYGB in participants with and without type 2 diabetes

Variable	Baseline		6 Months			24 Months		
	n	Mean (95% CI)	*n*	Mean (95% CI)	*p* value (vs baseline)	*n*	Mean (95% CI)	*p* value (vs baseline)
Basal beta cell responsivity (Φb), 10^{-9}								
With diabetes	39	34 (30, 39)	38	25 (21, 29)	<0.001	34	23 (20, 27)	<0.001
Without diabetes	18	41 (33, 49)	22	23 (20, 26)	<0.001	17	24 (19, 28)	<0.001
Dynamic beta cell responsivity (Φ_d), 10^{-9}								
With diabetes	39	2428 (1997, 2859)**	38	2181 (1793, 2569)	0.22	34	1967 (1496, 2439)	0.10
Without diabetes	18	4566 (3414, 5719)	22	2623 (2114, 3131)	<0.001	17	3120 (2442, 3798)**	0.017
Static beta cell responsivity (Φ_s), 10^{-9}/min								
With diabetes	39	97 (77, 117)***	38	125 (101, 150)**	0.004	34	106 (88, 125)***	0.41
Without diabetes	18	233 (183, 283)	22	212 (156, 267)	0.55	17	208 (175, 241)	0.36
Total Φ 10^{-9}/min								
With diabetes	39	100 (80, 120)***	38	131 (105, 156)**	0.01	34	111 (92, 130)***	0.38
Without diabetes	18	238 (188, 288)	22	218 (162, 274)	0.58	17	217 (183, 251)	0.45
$S_{I\text{-}MM}$, 10^{-5} l kg^{-1} min^{-1} (pmol/l)$^{-1}$								
With diabetes	33	5.6 (4.0, 7.1)	38	7.7 (6.0, 9.5)	0.023	34	9.4 (7.6, 11.2)	<0.001
Without diabetes	20	7.3 (3.0, 11.5)	22	10.7 (5.3, 16.0)	0.009	17	9.5 (6.3, 12.6)	0.16
DI_{MM} ($S_{I\text{-}MM}$ × total Φ)								
With diabetes	33	1022 (596, 1448)*	38	1639 (1170, 2108)*	0.037	34	1682 (1240, 2124)*	0.025
Without diabetes	18	2673 (1313–4034)	22	3224 (2103, 4345)	0.47	17	2866 (2070, 3663)	0.81
HE basal								
With diabetes	39	0.78 (0.75, 0.8)	38	0.86 (0.85, 0.88)	<0.001	34	0.88 (0.87, 0.89)	<0.001
Without diabetes	20	0.75 (0.72, 0.79)	22	0.86 (0.84, 0.87)	<0.001	17	0.88 (0.86, 0.9)	<0.001
HE total								
With diabetes	39	0.70 (0.68, 0.73)***	38	0.71 (0.68, 0.74)	0.43	34	0.72 (0.7, 0.75)	0.21
Without diabetes	20	0.62 (0.55, 0.69)	22	0.63 (0.58, 0.68)	0.7	17	0.66 (0.61, 0.72)	0.16

Estimates are based on Wald *t* test from generalised linear model

*$p < 0.05$, **$p < 0.01$ and ***$p < 0.001$ vs without diabetes

Although previously reported [18–21], in the largest studied groups to date after RYGB we found that fasting glucose and insulin levels declined, HbA_{1c} levels improved in both participants with and without diabetes to become nearly identical and not clinically meaningfully different, and a fundamental change in post-meal glucose appearance and disappearance was readily apparent. Through creation of a gastrojejunostomy that bypasses the pyloric valve, gastric emptying is accelerated [21–23] and peak postprandial glucose levels are shifted to an earlier time point after meal

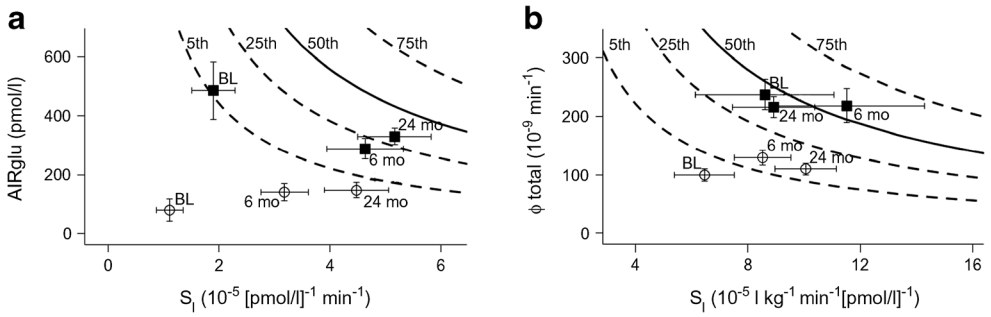

Fig. 4 Change in DI after RYGB for participants with (white circles) and without (black squares) type 2 diabetes at baseline (BL) and at 6 months (6 mo) and 24 months (24 mo) after RYGB. Mean ± SEM for AIRglu vs S_I derived from an FSIVGTT (**a**) and insulin secretion (Φ total) vs S_I derived from an MM (**b**). Background solid and dotted lines represent percentiles derived from normal populations as previously described [15, 47]

Table 5 Variables of insulin sensitivity and secretion derived from the insulin-modified FSIVGTT prior to and after RYGB in participants with and without type 2 diabetes

Variable	Baseline		6 Months			24 Months		
	n	Mean (95% CI)	*n*	Mean (95% CI)	*p* value (vs baseline)	*n*	Mean (95% CI)	*p* value (vs baseline)
AIRglu, pmol/l								
With diabetes	39	80 (8, 153)***	37	147 (91, 203)**	0.017	35	150 (101, 199)***	0.028
Without diabetes	22	486 (297, 674)	22	288 (221, 355)	0.008	17	312 (260, 363)	0.048
$S_{I\text{-}FSIVGTT}$, 10^{-5} $(pmol/l)^{-1}$ min^{-1}								
With diabetes	37	0.90 (0.60, 1.3)*	37	2.8 (2.2, 3.4)*	<0.001	34	4.3 (3.3, 5.3)	<0.001
Without diabetes	22	1.6 (1.1, 2.2)	22	4.2 (3.1, 5.2)	<0.001	17	5.0 (4.1, 5.9)	<0.001
S_G, min^{-1}								
With diabetes	27	14 (13, 16)	29	14 (13, 16)	0.94	26	15 (13, 16)	0.64
Without diabetes	19	15 (12, 17)	17	14 (12, 16)	0.88	15	16 (13, 19)	0.23
$DI_{FSIVGTT}$ ($S_{I\text{-}FSIVGTT}$ × AIRglu), min^{-1}								
With diabetes	39	73 (33, 114)***	37	326 (225, 427)***	<0.001	35	654 (307, 1000)***	0.001
Without diabetes	22	597 (407, 788)	22	957 (809, 1106)	0.002	17	1493 (1197, 1788)	<0.001

Estimates are based on Wald *t* test from generalised linear model

*$p < 0.05$, **$p < 0.01$ and ***$p < 0.001$ vs without diabetes

ingestion (30 min) in individuals with and without diabetes. Another notable finding was that, after surgery, peak postprandial glucose levels remained equal to baseline levels in the participants with type 2 diabetes and were actually higher than baseline in participants without diabetes. Additionally, postprandial glucose levels rapidly declined following these peaks in both groups, resulting in lower AUC glucose and HbA_{1c} levels during follow-up (i.e. improved glucose tolerance and glycaemic control, respectively). Such marked glucose fluctuations (including early postprandial hyperglycaemia), referred to as glycaemic variability or 'dysglycaemia', have been suggested to play a role in diabetes complications independently of HbA_{1c} levels [24]. However, several cohort studies that have included large numbers of post-RYGB participants have reported reduced microvascular and macrovascular diabetes-related complications and mortality compared with non-surgical control groups [25, 26], suggesting that despite this postprandial hyperglycaemia, the overall reductions in fasting and postprandial glucose exposure following RYGB are beneficial.

Plasma insulin responses, as well as those of GIP and GLP-1, were augmented in a pattern that mirrored the accelerated postprandial glucose appearance and disappearance following surgery. The seven- to eightfold increases in peak GLP-1 levels and GLP-1 AUC after surgery seen in both groups are thought to contribute to improved insulin secretion [27–30] and remained robust throughout the 24 months of follow-up. Counterintuitively, we found that despite large postsurgical weight loss and increases in peak insulin, glucose and GLP-1 levels [31, 32], the post-meal glucagon AUC did not change, and peak concentrations increased. This paradoxical meal-related glucagon response has previously been reported after RYGB in smaller studies [33–36] and in this report we confirm that this is not due to cross-reactivity of our assay with either GLP-1 or oxyntomodulin. Interestingly, our data are consistent with a recently demonstrated dual role for increased glucagon and GLP-1 levels in facilitating long-term weight-loss maintenance after RYGB through appetite regulation [37].

Insulin sensitivity measured during the FSIVGTT increased postoperatively in participants with and without diabetes. In agreement with our hypothesis and extending findings of a previous smaller study [38], the acute insulin response to intravenously administered glucose decreased in the non-diabetic participants but increased in those with type 2 diabetes up to 2 years after RYGB. Despite opposing stimulated insulin responses, RYGB restored diminished pancreatic insulin secretory capacity (as demonstrated by increases in $DI_{FSIVGTT}$) in both groups, with the non-diabetic group showing improvement from the fifth to the 25th percentile of normative population values. A larger relative increase in $DI_{FSIVGTT}$ occurred in the diabetes group, but the pre-surgery secretory defect was so profound that even with an approximately ninefold increase, the $DI_{FSIVGTT}$ still remained below the fifth percentile of the normal values 24 months after surgery. This meant that, despite equal weight loss, similarly impressive gains in insulin sensitivity by 24 months and less 'glucotoxicity' [39], the insulin secretory capacity of participants with type 2 diabetes did not recover fully enough after 2 years to even match the pre-surgical values of non-diabetic participants. Likewise, proinsulin levels and insulin-processing efficiency improved in both groups after surgery but still showed persistent defects (higher levels of proinsulin

and proinsulin:insulin ratio) in the type 2 diabetes group compared with the non-diabetic group at each visit.

Of note, 2 years after surgery, fasting plasma glucose or HbA_{1c} levels reverted to 'normal' in over 90% of the cohort with diabetes at baseline, becoming virtually indistinguishable from the non-diabetic control group. As already discussed, however, this does not mean that the groups became metabolically equivalent. Indeed, recent reports have shown that a persistent impairment in insulin secretion is a major factor contributing to the failure to achieve or sustain diabetes remission after surgically induced weight loss [40, 41]. These reports and our data indicate that simple clinical indicators used to determine normal glucose tolerance or 'non-diabetic' status in patients who have undergone weight loss surgeries fail to adequately describe the metabolic heterogeneity within this group or adequately assign risk for subsequent long-term deterioration in glucose control.

Previous studies have shown improvements of insulin secretion in response to both intravenous and oral (glucose and MM) challenges within 3 months of RYGB and biliopancreatic diversion [42, 43]. Longer-term, however, we find that the changes in insulin sensitivity and insulin secretion derived from the responses to an MM differed from the responses to an FSIVGTT. Basal insulin responsiveness (Φ_b) derived from the MM improved in both groups. However, despite a robust increase in postprandial GLP-1 levels that persisted for 2 years after RYGB, which should correspond with improved beta cell glucose sensitivity [6, 44–46], it is somewhat surprising that the corresponding measures of meal-related dynamic insulin responsiveness (Φ_d) did not change in the type 2 diabetes group and decreased in the non-diabetic control group, and that total insulin responsiveness (total Φ) did not change in either group. One potential explanation for this discrepancy between oral and intravenous stimulated insulin secretory responses is that Φ values are normalised to glucose levels during modelling of the MM data, whereas calculations of AIRglu from the FSIVGTT are not. Another explanation is that the Φ and S_I values derived during the MM were already close to population norms (see Fig. 4) in participants without diabetes, so did not have much room for improvement. It is also possible that improvements in $S_{I\text{-}MM}$ after surgery in the participants with type 2 diabetes group resulted in a reduced demand on islet cells, in which case maintenance of insulin responsiveness represents an improvement in the relative islet insulin secretory capacity, as reflected by a significant increase in DI_{MM} in this group.

In summary, we demonstrate that for up to 2 years after RYGB, obese adults experience improvements in S_I as well as improved insulin secretory responses to intravenously administered glucose as measured by DI with weight loss, despite opposite directionality of AIRglu responses in those with type 2 diabetes (increased) vs without diabetes (decreased). The gastric bypass procedure is therefore among a handful of interventions shown to reverse the decline in beta cell function that accompanies onset and progression of type 2 diabetes. For participants with type 2 diabetes, however, the baseline beta cell secretory defect was so profound that even with a marked postsurgical improvement, mean DI remained below the fifth percentile of a normative population 2 years after surgery. Combining our findings with recent reports that islet-cell recovery is an important determinant of diabetes remission status following bariatric surgery [40, 41, 46], consideration should be given to recommending RYGB as early as possible after the diagnosis of diabetes (the median diabetes duration in our study was only 3 years) or, more optimally, in obese individuals at risk for diabetes in whom we show that restoration of beta cell secretory capacity to variables within population norms is more likely. Our data also highlight a paradoxical increase in peak postprandial glucagon levels that, rather than negatively affecting postprandial glucose metabolism, supports an alternative, beneficial role for glucagon (along with markedly higher meal-stimulated GLP-1 levels) in appetite regulation and weight-loss maintenance after RYGB. Finally, studying the durability of beta cell recovery during longer-term follow-up will be vital for a deeper understanding of the mechanisms involved in type 2 diabetes improvement, remission and recurrence following RYGB.

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Data availability The datasets generated during and/or analysed during the current study are available by request from the National Institutes of Health (NIH)/National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (https://www.niddkrepository.org/home/).

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Duality of interest JQP receives consultant income for services on an advisory board for Novo Nordisk and receives grant funding from the NIH. CC holds ten patents and patent applications related to glucose sensors and artificial pancreas, received non-financial support from Roche and Dexcom, Inc., research support from Dexcom, Inc., Sanofi Aventis and Adocia and consultant income for services on an advisory board for Novo Nordisk. From 2007–2017, DEK was a full-time employee of Merck & Co. Inc., receiving salary and stock, but is now retired. DEC receives research support from Johnson & Johnson, the NIH and Medtronic. DRF receives consulting fees from Pacira Pharm and Patient Centered outcomes with Surgical Consulting LLC. APC receives grant support from the NIH and Covidien/Ethicon J&J. All other authors declare that there is no duality of interest associated with their contribution to this manuscript.

Contribution statement JQP contributed to study design, data acquisition and data analysis. GSJ, ASW, CDM, FP, CC, and RLP analysed data. KEF-S contributed to data acquisition. BHG, PJH, DEK, MAS, DEC, DRF and APC contributed to study conception and design. BMW contributed to study design and data acquisition. All authors contributed to the drafting and revision of this manuscript and provided approval of this final version. JQP is the guarantor of this work.

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