Roux-en-Y Gastric Bypass and Sleeve Gastrectomy: Mechanisms of Diabetes Remission and Role of Gut Hormones

M. Nannipieri, S. Baldi, A. Mari, D. Colligiani, D. Guarino, S. Camastra, E. Barsotti, R. Berta, D. Moriconi, R. Bellini, M. Anselmino, and E. Ferrannini

Department of Clinical and Experimental Medicine (M.N., S.B., D.C., D.G., S.C., E.B., D.M., R.Bel., E.F.), University of Pisa, 56126 Pisa, Italy; Consiglio Nazionale delle Ricerche Institute of Biomedical Engineering (A.M.), 35137 Padua, Italy; and Division of Bariatric Surgery (R.Ber., M.A.), Azienda Ospedaliera Universitaria Pisana, 56124 Pisa, Italy

Context: In obese patients with type 2 diabetes (T2DM), Roux-en-Y-gastric-bypass (RYGB) and sleeve gastrectomy (SLG) improve glycemic control.

Objective: The objective of this study was to investigate the mechanisms of surgery-induced T2DM improvement and role of gastrointestinal hormones.

Patients, Setting, and Intervention: In 35 patients with T2DM, we performed a mixed-meal test before and 15 days and 1 year after surgery (23 RYGB and 12 SLG).

Main Outcome Measures: Insulin sensitivity, β-cell function, and amylin, ghrelin, PYY, pancreatic polypeptide (PP), glucagon, and glucagon-like peptide-1 (GLP-1) responses to the meal were measured.

Results: T2DM remission occurred in 13 patients undergoing RYGB and in 7 patients undergoing SLG. Similarly in the RYGB and SLG groups, β-cell glucose sensitivity improved both early and long term ($P < .005$), whereas insulin sensitivity improved long term only ($P < .006$), in proportion to body mass index changes ($P < .001$). Early after RYGB, glucagon and GLP-1 responses to the meal increased, whereas the PP response decreased. At 1 year, PYY was increased, and PP, amylin, ghrelin, and GLP-1 were reduced. After SLG, hormonal responses were similar to those with RYGB except that PP was increased, whereas amylin was unchanged. In remitters, fasting GLP-1 was higher ($P = .04$), but its meal response was flat compared with that of nonremitters; postsurgery, however, the GLP-1 response was higher. Other hormone responses were similar between the 2 groups. In logistic regression, presurgery β-cell glucose sensitivity (positive, $P < .0001$) and meal-stimulated GLP-1 response (negative, $P = .004$) were the only predictors of remission.

Conclusions: RYGB and SLG have a similar impact on diabetes remission, of which baseline β-cell glucose sensitivity and a restored GLP-1 response are the chief determinants. Other hormonal responses are the consequences of the altered gastrointestinal anatomy. (*J Clin Endocrinol Metab* **98:** 4391–4399, 2013)

β-Cell dysfunction and insulin resistance are the main pathophysiological defects responsible for the development of hyperglycemia (1) and predict incident dia-

betes (2). Bariatric surgery induces remission of type 2 diabetes (T2DM) with high frequency (3, 4) and can prevent or delay incident T2DM (5). Roux-en-Y gastric by-

Abbreviations: AUC, area under the curve; BMI, body mass index; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; HbA$_{1c}$, glycosylated hemoglobin; MMT, mixed-meal test; OGTT, oral glucose tolerance test; PP, pancreatic polypeptide; RYGB, Roux-en-Y-gastric-bypass; SLG, sleeve gastrectomy; T2DM, type 2 diabetes mellitus.

pass (RYGB) is the most widely used bariatric procedure; typically, it results in major weight loss with no relevant malabsorptive symptoms. In a large meta-analysis, RYGB was reported to improve glycemic control in 80% of patients with T2DM (3). More recently, Schauer et al (6) reported that about 30% of patients with T2DM discontinued all antidiabetic medication after RYGB following hospital discharge. Several hypotheses have been put forward to explain the improvement in glycemic control after RYGB, including the starvation-followed-by-weight-loss hypothesis, the neuronal hypothesis, the foregut/hindgut hypothesis, and the ghrelin hypothesis (7, 8). However, at present, none of these explanations has been conclusively proven.

There is increasing favor for sleeve gastrectomy (SLG), which produces an early improvement in glucose homeostasis similar to that with RYGB (9–11). In this case too, the mechanisms of improvement in glucose metabolism remain uncertain. In fact, although foregut exclusion does not play a role in SLG, unexpected changes in distal intestinal hormones follow the operation despite the absence of gut manipulation (12–14). However, the mechanisms for these changes are not completely understood. Recently, it has been hypothesized that changes in ghrelin levels after SLG might help to explain the improvement in glucose metabolism (15, 16), but experimental data showing a direct effect of ghrelin on glycemic control in humans are lacking.

Collectively, these observations clearly suggest that different mechanisms could participate in the improvement/remission of T2DM after bariatric surgery. The objective of the present study, therefore, was to investigate the extent, time course, and mechanisms of recovery of β-cell function and insulin sensitivity in severely obese patients with T2DM undergoing RYGB or SLG. In particular, our goal was to investigate the differential role of gut hormones in the surgery-induced changes in insulin action/secretion while controlling for the effects of caloric restriction.

Materials and Methods

Subjects

The study group included 35 patients with T2DM (24 women and 11 men), who were wait-listed for laparoscopic RYGB (23 subjects) or SLG (12 subjects). Diabetes was diagnosed according to American Diabetes Association criteria (17). Antidiabetic treatment was insulin in 9 patients (40–120 IU/d), oral antidiabetic agents in 23 patients (sulfonylurea plus metformin), and diet alone in 3 patients. Exclusion criteria were (1) medical conditions requiring acute hospitalization, (2) blindness, and (3) severe medical conditions described elsewhere (18). Body composition was measured by electrical bioimpedance (Tanita BC418MA; Sensormedics Italia Srl).

The protocol was approved by the local ethics committee, and all patients signed a consent form before the study.

Study design

After screening, patients were admitted to our hospital ward for a period of 8 days; clinical parameters were measured daily. After an overnight fast, samples were obtained for routine blood chemistry, plasma glucose, and glycosylated hemoglobin (HbA_{1c}) concentrations. Then a standard oral glucose tolerance test (OGTT) (75 g of glucose in water) was performed (T1). All patients were then given a semiliquid, hypocaloric diet (1200 kcal; 18% protein, 29% fat, and 53% carbohydrate) for a period of 7 days. This diet was the same as the one that both patients undergoing either RYGB or SLG were to follow from the 5th to the 30th postoperative day. Oral antidiabetic agents were stopped 48 hours before the diet was started. If daylong plasma glucose concentrations were <10.0 mmol/L, patients were maintained with diet only; otherwise insulin was used to maintain plasma glucose <10.0 mmol/L. In patients who were taking insulin before hospitalization, injections were discontinued 16 hours before the metabolic study; patients taking glargine at bedtime were switched to NPH 2 days before the study. At the end of this presurgery diet period (T2), a mixed-meal test (MMT) (see below) was performed to evaluate β-cell function, peripheral insulin sensitivity, and hormonal responses. Patients were then discharged and for the following month were allowed to consume a free diet. SLG was performed on the basis of age (>55 years), vitamin (group B) and iron concentrations, intake of drugs with prevalent duodenal absorption, intestinal metaplasia, or relapse of *Helicobacter pylori* infection.

On the day of surgery, an insulin infusion was started in patients with a fasting plasma glucose concentration of >8.0 mmol/L to maintain the plasma glucose concentration between 6.0 and 10.0 mmol/L during surgery and for the following days. After surgery, the MMT was repeated 15 days (T3) and 1 year later (T4), whereas the OGTT was repeated at 1 year only. Diabetes remission (partial remission by American Diabetes Association criteria) was defined as a HbA_{1c} <6.5%, fasting glucose <7.0 mmol/L, and 2-hour glucose <11.1 mmol/L on the OGTT while not receiving antidiabetic treatment.

Laparoscopic RYGB

Laparoscopic RYGB was performed as described elsewhere (18).

Laparoscopic SLG

A four-fifths vertical gastrectomy was performed on a 34-French bougie using multiple reinforced 60-mm linear stapler firings starting 4 to 6 cm from the pylorus up to the gastroesophageal junction to obtain a 80- to 100-mL gastric tubule.

MMT

After an overnight (10–12 hours) fast, patients ingested a semiliquid meal (26% protein, 28% fat, and 45% carbohydrate; 350 kcal in total). Blood samples were collected through an indwelling cannula at times −30, 0 (time of the meal), +10, +20, +30, +45, +60, +90, +120, +150, +180, +240, and +300 minutes for the measurement of plasma glucose, insulin, C-peptide, glucagon, amylin, des-acyl ghrelin, pancreatic polypeptide (PP), PYY, and glucagon-like peptide-1 (GLP-1).

Methods

The plasma glucose concentration was measured on a Beckman Glucose Analyzer 2 (Beckman). Plasma insulin and C-peptide were measured by electrochemiluminescence on a Cobas e411 instrument (Roche Diagnostics S.p.A.). Plasma glucagon, PYY_{1-36}, PP, amylin, and des-acyl ghrelin concentrations were measured by Milliplex Mag kits (Millipore Corporation) on a Bio-Plex 200 system (Bio-Rad Laboratories, Inc). Plasma total GLP-1 concentrations were measured by ELISA (Millipore Corporation).

Modeling

β-Cell function parameters were derived from mathematical modeling of the plasma glucose, insulin, and C-peptide concentrations measured during the MMT (19). Insulin sensitivity was estimated as the Matsuda index, which estimates plasma glucose clearance rate at a level of hyperinsulinemia in the range of that achieved during a standard ($240 \, pmol \cdot min^{-1} \cdot m^{-2}$) euglycemic-hyperinsulinemic clamp, against which this index has been validated (20, 21).

The β-cell function model consists of 3 blocks: (1) a model for fitting the glucose concentration profile, the purpose of which is to smooth and interpolate plasma glucose concentrations; (2) a model describing the dependence of insulin (or C-peptide) secretion on the glucose concentration; and (3) a model of C-peptide kinetics, ie, the two-exponential model proposed by Van Cauter et al (22), in which the model parameters are individually adjusted to the subject's anthropometric data. Details are described elsewhere (18).

Statistical analysis

Results are expressed as means ± SD or median (interquartile range), for variables with normal or skewed distribution, respectively. Group differences were compared by the χ^2 test for categorical variables, by the Mann-Whitney U test for continuous variables, and by the Wilcoxon signed rank test for paired data. Analysis of changes over time (early or late after surgery vs presurgery) was performed by ANOVA for repeated measures; for this test, parameters with a skewed distribution were log-transformed. The output of this ANOVA model is a P value for the time factor (ie, overall changes over time), a P value for the group (ie, between-group differences), and a P value for the time × group interaction (ie, differential changes between groups over time). A multivariate regression model was used to analyze correlations among variables. A value of $P < .05$ was considered significant.

Results

Clinical results (OGTT)

Before surgery, patients undergoing SLG were significantly, if slightly, more obese than the RYGB group, but otherwise similar in age, HbA_{1c}, duration of diabetes, and fasting and 2-hour plasma glucose (see Supplemental Table 1 published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org.). The small drop in body mass index (BMI) seen at 15 days in both groups was accounted for by loss of both body fluids and fat mass (Table 1). One year after surgery, BMI and HbA_{1c} had decreased similarly in both groups (Table 1). On the OGTT, both fasting and 2-hour plasma glucose concentrations were markedly reduced with both kinds of sur-

Table 1. Clinical and Metabolic Characteristics of the Study Subjects Before and 15 Days and 1 Year After Surgery

	RYGB			SLG		
	Pre (T2)	15 d (T3)	1 y (T4)	Pre (T2)	15 d (T3)	1 y (T4)
No. of subjects	23	23	23	12	12	12
Weight, kg	113 ± 20	109 ± 20[a]	78 ± 13[a]	124 ± 18	121 ± 18[a]	95 ± 11[a]
Excess body weight, %[b,c]	107 ± 32	102 ± 32[a]	44 ± 21[a]	128 ± 35	127 ± 33[a]	80 ± 31[a]
Fat mass, %[c]	45.3 ± 4.0	43.9 ± 3.9[a]	29.8 ± 6.0[a]	47.1 ± 6.0	46.5 ± 6.0[a]	35.5 ± 8.6[a]
Total body water, kg[b]	44.2 ± 6.5	42.7 ± 6.2[a]	36.7 ± 5.5[a]	49.4 ± 7.0	47.7 ± 7.4[a]	42.9 ± 7.5[a]
BMI, kg/m²[b]	41.8 ± 5.4	40.4 ± 5.6[a]	28.9 ± 3.7[a]	46.4 ± 5.8	45.3 ± 5.9[a]	35.8 ± 5.2[a]
HbA_{1c}, %	8.2 ± 2.3		6.3 ± 0.9[a]	8.2 ± 1.5		6.7 ± 0.9[a]
Fasting glucose (MMT), mmol/L	8.6 ± 2.8	8.4 ± 3.3	6.1 ± 1.9[a]	7.8 ± 1.4	7.4 ± 3.0	5.8 ± 0.9[a]
Mean glucose (MMT), mmol/L	8.9 ± 2.3	9.1 ± 5.1	6.4 ± 1.9[a]	8.9 ± 1.9	7.7 ± 3.1	6.5 ± 1.3[a]
Fasting insulin (MMT), pmol/L[b]	72 (60)	90 (48)	42 (30)[a]	102 (78)	108 (42)	66 (30)[a]
Mean insulin (MMT), pmol/L[b]	660 (360)	690 (360)[a]	570 (276)[a]	1014 (984)	1026 (282)[a]	762 (426)[a]
Time to glucose peak, min	79 ± 42	40 ± 15[a]	34 ± 12[a]	86 ± 22	43 ± 12[a]	51 ± 15[a]
Insulin sensitivity, mL · min⁻¹ · m⁻²	3.3 (2.0)	4.3 (3.5)	6.7 (5.9)[a]	1.9 (1.1)	2.0 (1.0)	5.0 (2.3)[a]
Fasting insulin secretion, pmol · min⁻¹ · m⁻²[b]	88 (48)	103 (31)[a]	65 (31)[a]	110 (102)	182 (100)[a]	84 (31)[a]
Total insulin output, nmol · m⁻²[b]	35 (25)	45 (20)[a]	34 (23)	49 (42)	77 (34)[a]	37 (245)
β-Cell glucose sensitivity, pmol · min⁻¹ · m⁻² · mM⁻¹	24 (43)	26 (40)[a]	40 (73)[a]	34 (41)	38 (58)[a]	52 (41)[a]
Rate sensitivity, pmol · m⁻² · mM⁻¹	320 (643)	405 (904)[a]	714 (1159)[a]	735 (1448)	966 (2038)	800 (1462)
Insulin clearance, L · min⁻¹ · m⁻²[b]	1.13 (0.65)	1.28 (0.35)[a]	1.25 (0.60)[a]	1.03 (0.72)	1.15 (0.53)[a]	1.06 (0.59)[a]

Abbreviations: Pre, presurgery; 15 d, 15 days after surgery; 1 y, 1 year after surgery. Data are means ± SD or median (interquartile range).

[a] $P < .05$ or less vs T2 in each surgery group.

[b] $P < .05$ or less for the group factor (RYGB vs SLG).

[c] $P < .05$ or less for the time × group interaction.

gery. By defining partial remission as $HbA_{1c} <6.5\%$, fasting glucose <7.0 mmol/L, and 2-hour glucose <11.1 mmol/L with no antidiabetic treatment, diabetes remission was seen in 20 of the 35 patients at 1 year postsurgery (13 RYGB and 7 SLG); this left 15 patients in whom diabetes was still improved but not in partial remission even at 1 year.

Metabolic results (MMT)

After meal ingestion, neither fasting nor mean glucose levels changed at 15 days, whereas both were significantly decreased at 1 year. The time to glucose peak, which averaged ~80 minutes before surgery, occurred at significantly earlier times both 15 days and 1 year postsurgery, similarly for RYGB and SLG (Figure 1 and Table 1).

Baseline insulin sensitivity, insulin clearance, and β-cell glucose sensitivity were similar between the 2 groups, whereas fasting and total insulin secretion were higher in the SLG group than in the RYGB group. Fasting insulin secretion increased early and declined 1 year postsurgery in both groups, whereas total insulin output increased early and then returned to presurgery levels at 1 year. The

estimated insulin sensitivity improved long term (but not at 15 days) after surgery in both the RYGB and SLG groups, and the 1-year changes in insulin sensitivity correlated with the corresponding changes in BMI ($r = 0.51$, $P <.001$) with no significant difference between the RYGB and SLG groups (Figure 2) In contrast, β-cell glucose sensitivity showed an early improvement in both groups; the values at 1 year were not significantly different from those at 15 days (Supplemental Figure 1). Likewise, rate sensitivity increased early postsurgery and was sustained at 1 year. Insulin clearance increased immediately after surgery but not at the later time, the changes being more pronounced in the RYBG group than in the SLG group (Table 1).

Effects of RYGB on gastrointestinal (GI) hormones (Table 2 and Supplemental Figure 2A)

Early after surgery, fasting plasma concentrations of PP, glucagon, and GLP-1 increased; in contrast, the PP response to the meal (as the area under the curve [AUC] or the incremental AUC) decreased, whereas the glucagon and GLP-1 responses increased. At 1 year, PP behaved as
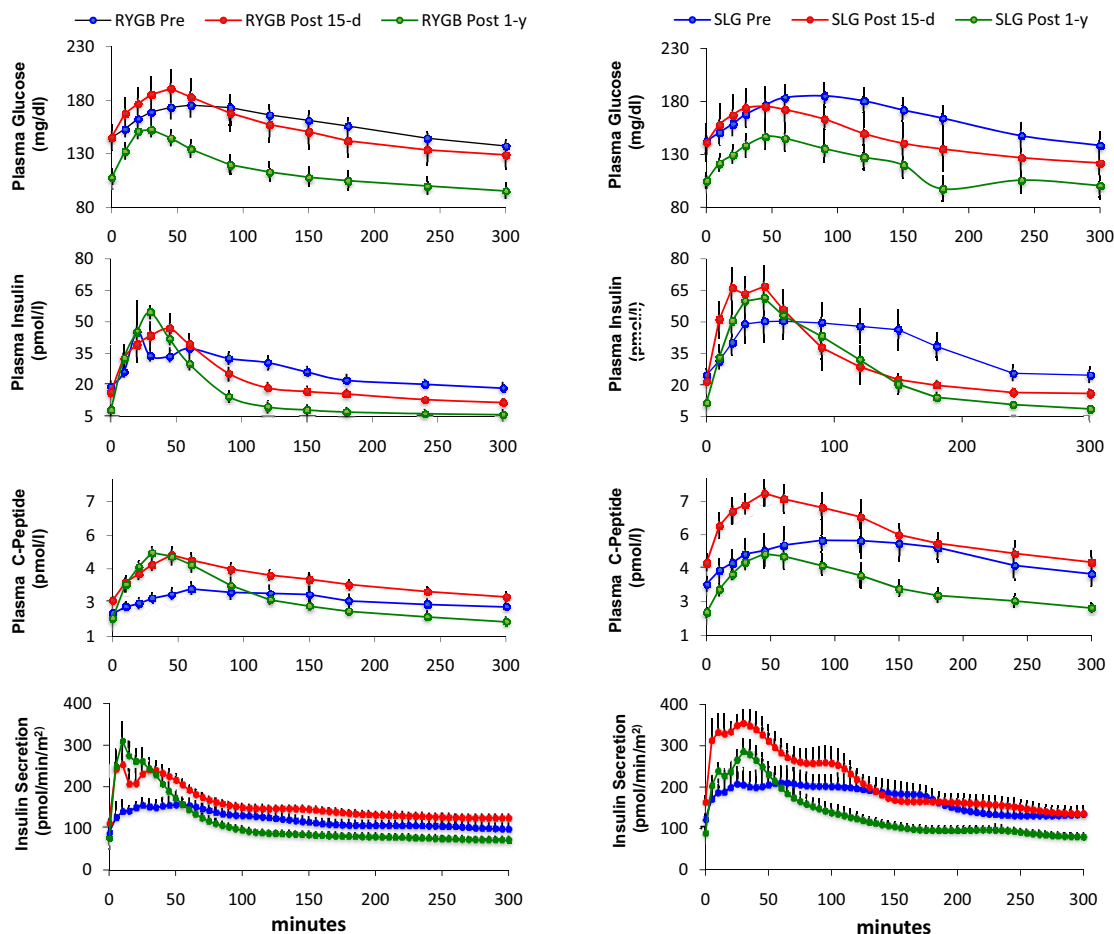
Figure 1. Plasma glucose, insulin, and C-peptide concentrations and insulin secretion during MMT in patients undergoing RYGB and SLG before and 15 days and 1 year after surgery. Plots are means ± SEM.
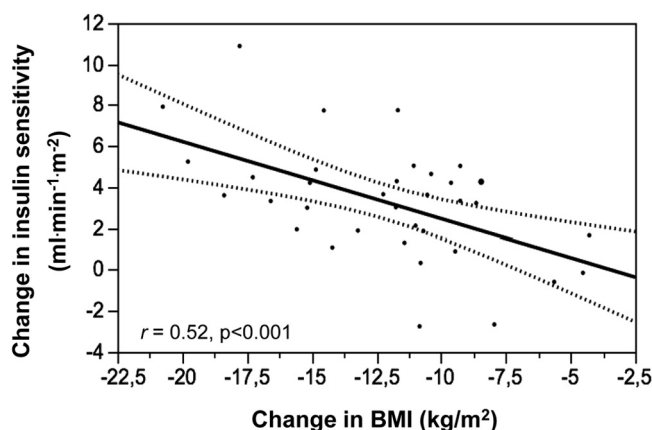
Figure 2. Consensual changes in BMI and insulin sensitivity in patients undergoing RYGB and SLG, before and 15 days and 1 year after surgery. Plots are means ± SD.

at 15 days; fasting and stimulated amylin and ghrelin were reduced, whereas the GLP-1 pattern was flattened. Plasma PYY was increased both in the fasting state and in response to the meal.

Effects of SLG on GI hormones (Table 2 and Supplemental Figure 2B)

The pattern of hormonal response was similar to that seen with RYGB, with the following exceptions. Plasma PP, fasting as well as stimulated, was significantly higher than with RYGB, whereas plasma amylin was not affected by surgery either acutely or chronically.

Correlations between metabolic variables and GI hormones (Supplemental Table 2)

To explore the impact of hormonal responses (AUCs) on relevant physiological parameters (ie, HbA_{1c}, insulin sensitivity, and β-cell glucose sensitivity), we computed the matrix of Spearman correlation coefficients. The first important finding is that the degree of obesity itself, as indexed by the BMI, was associated not only with the plasma insulin response (positively) and insulin sensitivity (negatively) but also with the glucagon, amylin, PP, and ghrelin responses in a direct fashion and with the PYY response in a negative fashion. Therefore, using a multivariate model, the relationships of interest were adjusted for BMI and type of surgery (RYGB or SLG, included as a fixed factor). The results show that β-cell glucose sensitivity was independently influenced only by the GLP-1 response in a positive manner, and insulin sensitivity was independently enhanced only in association with a higher PYY response. HbA_{1c} was inversely related to both insulin sensitivity (through the BMI) and glucose sensitivity. The type of surgery was only associated with the PP response, which was higher in more insulin-resistant subjects after SLG but not after RYGB.

In a multivariate regression model including age and BMI, β-cell glucose sensitivity was negatively associated with HbA_{1c} values (partial $r = -0.39$, $P < .0001$), diabetes duration (partial $r = -0.34$, $P = .0006$), and the GLP-1 response (partial $r = 0.23$, $P < .02$; total $r = 0.61$, $P < .0001$).

Table 2. GI Hormones Presurgery and 15 Days and 1 Year After Surgery

	RYGB			SLG		
	Pre (T2)	15 d (T3)	1 y (T4)	Pre (T2)	15 d (T3)	1 y (T4)
Fasting amylin, pg · mL^{-1}	83 (42)	80 (40)	38 (18)[a]	38 (38)	36 (28)	38 (11)
Fasting ghrelin, pg · mL^{-1}	32 (14)	28 (25)	24 (16)[a]	26 (5)	25 (3)	12 (12)[a]
Fasting PP, pg · mL^{-1b}	66 (44)	72 (69)[a]	86 (80)[a]	64 (141)	102 (162)[a]	154 (242)[a]
Fasting PYY, pg · mL^{-1}	75 (61)	71 (59)	119 (72)[a]	58 (43)	63 (38)	69 (82)[a]
Fasting glucagon, pg · mL^{-1}	60 (22)	72 (29)[a]	52 (46)	48 (35)	72 (51)[a]	58 (37)
Fasting GLP-1, pM	26 (16)	31 (17)[a]	19 (14)[a]	22 (20)	34 (17)[a]	23 (11)
AUC$_{Amylin}$, ng · mL^{-1b}	20.3 (13.2)	21.1 (10.5)	9.5 (6.0)[a]	9.1 (5.7)	10.3 (5.9)	12.5 (11.8)
ΔAUC$_{Amylin}$, ng · mL^{-1b}	1.5 (3.3)	2.9 (11.2)	0.5 (3.6)[a]	0.1 (3.2)	0.8 (2.2)	1.4 (15.8)
AUC$_{Ghrelin}$, ng · mL^{-1}	0.71 (0.60)	0.68 (0.89)	0.47 (0.19)[a]	0.62 (0.09)	0.61 (0.07)	0.29 (0.19)[a]
ΔAUC$_{Ghrelin}$, ng · mL^{-1}	−0.3 (1.3)	0.2 (0.5)	−0.8 (1.8)	−0.04 (1.3)	−0.8 (1.1)	0.09 (1.0)
AUC$_{PP}$, ng · mL^{-1b}	60.7 (65.8)	19.9 (27.6)[a]	27.6 (41.5)[a]	91.7 (5.5)	112.0 (6.3)[a]	95.2 (21.5)
ΔAUC$_{PP}$, ng · mL^{-1b}	46.0 (57.2)	5.6 (12.4)[a]	9.2 (25.6)[a]	49.4 (63.1)	90.6 (19.3)[a]	73.4 (155.6)[a]
AUC$_{PYY}$, ng · mL^{-1}	18.0 (6.7)	24.0 (10.6)	34.0 (33.3)[a]	13.9 (3.4)	13.9 (3.5)	21.0 (18.8)[a]
ΔAUC$_{PYY}$, ng · mL^{-1}	0.9 (11.8)	3.2 (14.5)	5.3 (17.2)[a]	1.0 (5.4)	−1.0 (8.4)	4.3 (13.1)[a]
AUC$_{Glucagon}$, ng · mL^{-1}	16.5 (8.9)	22.5 (15.1)[a]	14.5 (6.1)	20.1 (8.9)	23.6 (18.8)[a]	14.2 (5.8)
ΔAUC$_{Glucagon}$, ng · mL^{-1}	3.1 (4.9)	7.1 (10.3)[a]	2.7 (7.5)	5.2 (10.2)	6.3 (18.3)[a]	0.8 (5.1)
AUC$_{GLP-1}$, nM	9.3 (3.9)	12.3 (3.5)[a]	7.6 (4.5)	7.3 (7.6)	11.1 (7.5)[a]	8.3 (2.1)
ΔAUC$_{GLP-1}$, nM	2.3 (2.0)	4.2 (2.3)[a]	3.1 (3.1)	2.1 (3.3)	3.8 (3.4)[a]	3.5 (3.4)

Abbreviations: Pre, presurgery; 15 d, 15 days after surgery; 1 y, 1 year after surgery. Data are means ± SD or median (interquartile range).

[a] $P < .05$ or less for the time factor.

[b] $P < .05$ or less for the time × group interaction.

Diabetes remission (Table 3 and Supplemental Table 3)

Age, initial BMI, and the kind of surgery did not distinguish remitters from nonremitters. Duration of diabetes (6 ± 4 vs 12 ± 5 years, $P < .0001$), baseline HbA$_{1c}$ (7.5 ± 1.4 vs $9.2 \pm 2.4\%$, $P < .01$), mean plasma glucose levels ($P = .001$), and β-cell glucose sensitivity ($P = .002$) were all worse in nonremitters than in remitters. Fasting insulin secretion was higher in remitters than in nonremitters ($P < .05$). Before surgery, the time to plasma glucose peak during the MMT was shorter in remitters than in nonremitters ($P = .03$), but after surgery it was anticipated in both groups. Although all metabolic parameters showed an improvement postsurgery, the extent of the improvement was significantly less in nonremitters than in remitters for mean glucose levels, insulin sensitivity, and β-cell glucose sensitivity.

With regard to hormones, before surgery, fasting levels of GLP-1 were higher ($P = .04$), whereas fasting glucagon ($P = .04$) and amylin levels ($P < .05$) were lower in remitters than in nonremitters; the surgery-induced changes in fasting hormone concentrations, however, did not differ between the 2 groups. The meal-induced incremental hormone responses were similar between remitters and non-remitters, except for GLP-1, which was blunted in remitters at baseline and higher in remitters than in nonremitters at both the early and late times postsurgery (Figure 3).

When predictors of diabetes remission were sought in a logistic regression model, presurgery β-cell glucose sensitivity (positive, $P < .0001$) and presurgery incremental GLP-1 response (negative, $P = .004$) were the only variables significantly associated with partial diabetes remission at 1 year.

Discussion

The key features of the present study design were (1) the use of a physiological stimulus, the mixed meal, after 1 week of a low-calorie diet: this was done to reduce the impact of calorie deprivation in the early postsurgical period, and (2) the comparison of 2 bariatric operations, only one of which involves bypassing the duodenum. From the joint analysis of these data we aimed to assess the role of multiple hormonal changes, alterations of food transit, and weight loss itself as the main determinants of glucose tolerance, namely, insulin sensitivity and β-cell function.

Table 3. Metabolic Parameters of the Study Subjects Presurgery and 15 Days and 1 Year After Surgery

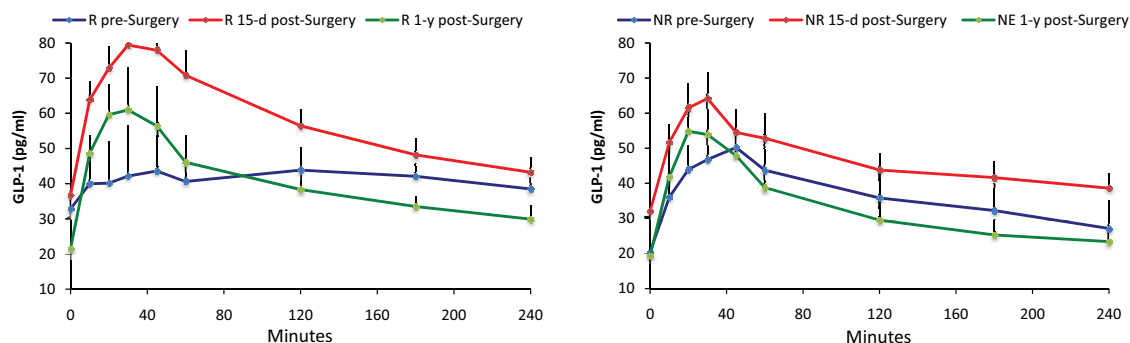|	Remitters			Nonremitters		
	Pre	15 d	1 y	Pre	15 d	1 y
No. of subjects	20	20	20	15	15	15
Glucose, mM[a,b,c,d]	7.9 (2.1)	6.1 (0.8)	5.5 (0.5)	9.5 (4.1)	10.9 (4.6)	7.4 (1.7)
Time to glucose peak, min[a,b,d]	70 ± 33	39 ± 13	34 ± 10	97 ± 36	44 ± 15	48 ± 17
Insulin sensitivity, mL $\cdot$ min^{-1} $\cdot$ m^{2a,c}	3.3 (2.0)	4.3 (3.5)	6.7 (5.9)	1.9 (1.1)	2.0 (1.0)	5.0 (2.3)
Fasting insulin secretion, pmol $\cdot$ min^{-1} $\cdot$ m$^{-2a,d}$	101 (78)	111 (69)	76 (36)	72 (43)	104 (46)	78 (47)
Total insulin output, nmol $\cdot$ m$^{-2a,c}$	38 (37)	49 (33)	35 (20)	27 (15)	52 (23)	37 (30)
β-Cell glucose sensitivity, pmol $\cdot$ min^{-1} $\cdot$ m^{-2}/mM^{a,b,d}	30 (36)	52 (72)	75 (58)	11 (10)	18 (11)	19 (26)
Fasting GLP-1, pM[a,b,d]	29 (16)	33 (2)	22 (20)	18 (13)	34 (13)	19 (9)
Fasting glucagon, pg $\cdot$ mL$^{-1a,b}$	50 (16)	71 (12)	56 (36)	66 (39)	87 (67)	62 (47)
Fasting PYY, pg $\cdot$ mL^{-1a}	69 (51)	80 (55)	95 (79)	71 (53)	63 (31)	134 (85)
Fasting PP, pg $\cdot$ mL^{-1a}	71 (58)	92 (113)	102 (77)	64 (115)	78 (194)	116 (197)
Fasting ghrelin, pg $\cdot$ mL^{-1a}	28 (8)	28 (6)	19 (19)	29 (22)	28 (22)	17 (13)
Fasting amylin, pg $\cdot$ mL$^{-1a,b,d}$	43 (55)	53 (37)	38 (14)	87 (44)	80 (37)	39 (14)
ΔAUC$_{GLP-1}$, nM[a,c]	2.14 (1.86)	5.48 (2.02)	3.64 (3.30)	2.80 (4.73)	3.55 (1.91)	1.79 (2.70)
ΔAUC$_{Glucagon}$, ng $\cdot$ mL^{-1}	3.05 (4.88)	6.30 (13.06)	2.37 (7.11)	5.28 (10.02)	7.06 (19.61)	2.05 (8.17)
ΔAUC$_{PYY}$, ng $\cdot$ mL^{-1}	1.17 (7.13)	3.25 (11.03)	3.61 (13.61)	-0.8 (10.46)	1.86 (8.41)	6.25 (21.17)
ΔAUC$_{PP}$, pg $\cdot$ mL^{-1}	58.3 (78.5)	19.7 (66.3)	10.6 (27.3)	24.4 (37.9)	12.3 (95.1)	25.4 (75.3)
ΔAUC$_{Ghrelin}$, pg $\cdot$ mL^{-1a}	-50 (560)	47 (577)	-321 (2322)	-595 (1711)	90 (1037)	-488 (740)
ΔAUC$_{Amylin}$, pg $\cdot$ mL^{-1}	1.48 (2.25)	1.31 (4.24)	1.43 (4.77)	0.21 (4.92)	1.98 (10.02)	0.27 (12.61)

Abbreviations: Pre, presurgery; 15 d, 15 days after surgery; 1 y, 1 year after surgery. Data are means $\pm$ SD or median (interquartile range).

[a] $P < .05$ or less for the time factor.

[b] $P < .05$ or less for the group factor (RYGB vs SLG).

[c] $P < .05$ or less for the time $\times$ group interaction.

[d] $P < .05$ or less between Pre vs 15 d.

Figure 3. Plasma GLP-1 curves during MMT in remitters (R) and nonremitters (NR) before and 15 days and 1 year after surgery. Plots are means ± SEM.

The major findings at 15 days after surgery were the following: (1) plasma glucose concentrations with consumption of the MMT were minimally affected, but peak levels were significantly anticipated with both interventions; (2) insulin concentrations and secretion rates were increased, (3) β-cell sensitivity and rate sensitivity were modestly improved; and (4) glucagon and the GLP-1 response were heightened. The above results applied equally to RYGB and SLG. Thus, after surgery, gastric emptying is accelerated also with SLG, in which the pyloric sphincter is intact, suggesting a change in the neural control of gastric peristalsis consequent upon gastric resection (23). After RYGB, the bulk of foods pass without hindrance into the small intestine, whereas small intestinal transit is prolonged (24); similar data have been reported after SLG. This accelerated transit accounts for the anticipated glucose peak and, consequently, for the changes in the time course of insulin secretion. Furthermore, when the impact of acute calorie restriction was minimized, insulin sensitivity was unchanged and the absolute insulin release was slightly increased, possibly as a carryover of the recent surgical stress. β-Cell function was modestly improved, especially in terms of rate sensitivity as a consequence of the more rapid glucose rise and, presumably, the higher GLP-1 response. The early and prolonged contact of food with the distal small bowel mucosa may explain the enhanced GLP-1 release. The reason for the increased glucagon response, which has been observed by others (25–27), in the face of similar glucose and higher insulin concentrations, remains undetermined, however.

Under the circumstances, the presence of a duodenojejunal bypass (RYGB) did not appear to exert any detectable effect.

The major findings 1 year after surgery were the following: (1) body weight was markedly reduced, somewhat more with RYGB than with SLG ($P = .09$ for the time × surgery interaction); (2) as judged from the plasma glucose profiles, gastric transit was still accelerated in both surgery groups; (3) glycemic control, as indexed by HbA_{1c}, fasting, and mean plasma glucose levels with the MMT, improved

to a similar extent after RYGB and SLG; the number of remitters was similar between the 2 operations; (4) fasting insulin secretion was reduced, and total insulin output was back to baseline levels; (5) insulin sensitivity was improved essentially in proportion to the change in BMI (Figure 2), and (6) β-cell glucose sensitivity was further improved compared with that at 15 days postsurgery.

With regard to the hormonal changes, glucagon and GLP-1 responses at 1 year were attenuated with both surgical procedures, ie, the responses at 15 days. This finding is at partial variance with data in the literature (26–29); we hypothesize that one possible reason is the different composition of the mixed meal, in particular the presence of fructose (45 g) rather than glucose in the meal we used. In addition, PYY responses were increased with RYGB as well as with SLG, and ghrelin responses were decreased with both surgical procedures. With the exception of GLP-1, all these hormonal profiles were positively associated with the observed BMI in the entire dataset, suggesting that their changes with time were the result of weight loss rather than the kind of surgical procedure. In contrast, amylin decreased only with RYGB, whereas PP responses increased with SLG but decreased with RYGB.

This GI hormonal pattern must be interpreted both in terms of its origin and its impact on glucose tolerance. The reduction in ghrelin concentrations, which has been noted before (12, 14), presumably results from the reduction of ghrelin-producing cells, by gastrectomy in the case of SLG, and by exclusion of most of the stomach from food contact in the case of RYGB. In the latter, weight loss restores the physiologic decrease in ghrelin that occurs with feeding.

Of the islet peptides, insulin, glucagon, amylin, and PP were interrelated in that they all were stimulated by a mixed meal. However, the effects of surgery on their responses were different, because amylin was markedly suppressed with RYGB but not with SLG, in both of which insulin release, after an early increase at 15 days, returned toward presurgery levels. Thus, whatever the mechanisms by which RYGB suppresses amylin release, it is clear that this hormone is not cosecreted with insulin consistently.

PP release, on the other hand, was up-regulated by SLG and down-regulated by RYGB. As for amylin, the underlying mechanisms are presently undefined; however, the divergent impact of surgery points toward the involvement of neural pathways, which the 2 operations disrupt or activate differentially. PYY was found to be increased only at 1 year in both groups. An increase in fasting and postprandial PYY after RYGB has been widely reported and has been interpreted as a mediator of the appetite reduction and of improved glycemic control (28, 29).

With regard to the influence of these hormonal changes on the determinants of glucose tolerance, our analysis indicates 3 plausible effects. First, the increase in glucagon opposes the suppressibility of endogenous glucose output by insulin, as we recently demonstrated with the use of a double tracer protocol in both nondiabetic and diabetic patients undergoing RYGB (30). Second, the increase in GLP-1 can be linked with the improved β-cell function, especially at the earlier postsurgical time. Finally, we did single out a weight-independent association between PYY responses and insulin sensitivity. In a recent study, low plasma PYY levels have been related to both insulin resistance and insulin hypersecretion; a relative lack of PYY has also been shown to alter the intrinsic properties of islets (31).

Further insight can be gained from the comparison of remitters and nonremitters (Table 3). As expected from previous studies (18), remitters were characterized by better baseline glycemic control, a shorter time to peak for glucose excursions, and better insulin sensitivity and β-cell function. In multivariate analysis, β-cell glucose sensitivity emerged as the chief predictor of remission, as was the case in a prior series (18).

Limitations of this study are the small number of patients in the SLG group, the lack of randomization, the relatively short follow-up, and the absence of a diet control group. There were, however, 2 novel findings. First, the kind of surgery seems to be unrelated to remission at 1 year, again suggesting that the duodenal bypass does not contribute independently to this outcome. Our data are in agreement with those of some authors (6, 32). However, Kashyap et al (33) have recently reported that the glycemic outcome at 2 years postsurgery was superior with RYGB vs that with SLG.

Second, the GLP-1 response at baseline was an *inverse* predictor of remission (independently of β-cell function), in that patients with a rather flat initial response underwent remission more often than those with a robust baseline response (Figure 3). It should be noted that, according to a recent meta-analysis (34), GLP-1 responses in type 2 diabetes are quite variable, perhaps as a function of the patient's phenotype but also because of other factors, in-

cluding impaired secretion (35, 36), accelerated metabolism of GLP-1 (37), and defective responsiveness to GLP-1 (38).

In summary, RYGB and SLG both cause marked metabolic adaptations, resulting in frequent diabetes remission 1 year later. When the confounding of calorie restriction is factored out, β-cell function improves rapidly, very possibly under the influence of enhanced GLP-1 responsiveness. The changes in other hormones (glucagon, amylin, ghrelin, PP, and PYY) appear to only reflect the anatomical rearrangement, the alteration of neural pathways, and weight loss itself. Insulin sensitivity improves in proportion to weight loss, with a possible involvement of PYY. The presence of the duodenojejunal bypass in RYGB does not appear to be directly responsible for any of the above metabolic adaptations.

Acknowledgments

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