Effects of Gastric Bypass and Gastric Banding on Glucose Kinetics and Gut Hormone Release

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Background: Bariatric surgery markedly improves glucose homeostasis in patients with type 2 diabetes even before any significant weight loss is achieved. Procedures that involve bypassing the proximal small bowel, such as Roux-en-Y gastric bypass (RYGBP), are more efficient than gastric restriction procedures such as gastric banding (GB).
Objective: To evaluate the effects of RYGBP and GB on postprandial glucose kinetics and gastro-intestinal hormone secretion after an oral glucose load.
Methods and Procedures: This study was a cross-sectional comparison among non-diabetic, weight-stable women who had undergone RYGBP (n = 8) between 9 and 48 months earlier or GB (n = 6) from 25 to 85 months earlier, and weight- and age-matched control subjects (n = 8). The women were studied over 4 h following ingestion of an oral glucose load. Total glucose and meal glucose kinetics were assessed using glucose tracers and plasma insulin, and gut hormone concentrations were simultaneously monitored.
Results: Patients who had undergone RYGBP showed a a more rapid appearance of exogenous glucose in the systemic circulation and a shorter duration of postprandial hyperglycemia than patients who had undergone GB and C. The response in RYGBP patients was characterized by early and accentuated insulin response, enhanced postprandial levels of glucagon-like peptide-1 (GLP-1) and polypeptide YY (PYY), and greater postprandial suppression of ghrelin.
Discussion: These findings indicate that RYGBP is associated with alterations in glucose kinetics and glucoregulatory hormone secretion. These alterations are probably secondary to the anatomic rearrangement of the foregut, given the fact that they are not observed after GB. Increased PYY and GLP-1 concentrations and enhanced ghrelin suppression are compatible with reduced food intake after RYGBP.

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INTRODUCTION

Recent studies have shown that bariatric surgery is not only highly efficient in promoting weight loss, but that it also leads to an improvement, or resolution of, most of the obesity-related co-morbidities (1–3). In particular, patients with diabetes mellitus show a marked improvement in glucose homeostasis after undergoing surgery for weight loss (4–9). In fact, most of the bariatric procedures commonly used worldwide have been shown to restore a normal glucose profile in many diabetes patients. However, meta-analysis suggests that procedures that involve bypassing the proximal small bowel, such as Roux-en-Y gastric bypass (RYGBP) and biliopancreatic diversion are more efficient than procedures involving gastric restriction only, such as gastric banding (GB) (1,3,10). On the basis of current reports, 80–100% of diabetes patients have normal glycemia after RYGBP and biliopancreatic diversion vs. 30–70% of patients after GB. Importantly, several studies have shown that the blood glucose profile is improved very early after surgery, long before any significant weight loss or fat reduction occurs (11–13), thereby indicating that weight loss (and, presumably, improved insulin sensitivity) is not the sole factor involved in achieving an improved glucose profile. However, the mechanisms whereby bariatric surgery improves glucose metabolism are not fully understood. Several recent reports indicate that gut hormone release is significantly altered after bypass of the proximal small bowel, secondary to exclusion of food from the intestinal transit (14,15). The ensuing pattern of gut hormone secretion may contribute not only to reduction in food intake but also to stimulation of insulin secretion (16–18). In addition, by altering gastric size and mobility, gastric surgery may significantly impact postprandial glucose absorption and kinetics.

In order to better understand the effects of bariatric surgery on glucose regulation we compared the effects of RYGBP and GB on postprandial glucose kinetics. For this purpose, we

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studied two groups of non-diabetic patients who had undergone successful RYGBP or GB some months to years earlier, and one group of weight-matched non-diabetic control subjects (C). In order to avoid the interference effects of negative energy balance, we studied the patients after their period of most rapid weight loss, when their body weights were stable. Exogenous glucose appearance (EGA) and endogenous glucose production were assessed using a dual glucose isotope method after a standardized glucose load. Plasma glucoregulatory hormone and gut hormone concentrations were simultaneously monitored.

METHODS AND PROCEDURES

Subjects

Three groups of female subjects were recruited to participate in this study: (i) patients who had undergone RYGBP (n = 8), (ii) patients who had undergone GB (n = 6), and (iii) non-operated control subjects (n = 8). The criteria for inclusion in the first two groups (post-surgery) were that the subjects had undergone the surgical procedure >9 months previously, had maintained a stable body weight (with weight variation <2 kg) for the past 3 months, and had no diabetes mellitus or impaired glucose tolerance before surgery. The interval between surgery and metabolic evaluation was 9–48 months in patients who had undergone RYGBP, and 25–85 months in patients who had undergone GB. Preoperative weight (RYGBP: 122.3 ± 8.9 kg, GB: 109.3 ± 2.1 kg, P = NS) and BMI (RYGBP: 44.9 ± 1.8 kg/m^2, GB: 41.1 ± 0.5 kg/m^2, P < 0.05), and weight loss after surgery (RYGBP: 47.8 ± 3.3 kg, GB: 32.4 ± 2.0 kg, P < 0.01) were all higher after RYGBP. The eight control subjects were recruited by advertisement, and were weight-matched to post-surgery RYGBP and GB patients. All the subjects were white women, with ages ranging from18–50 years. None of the subjects were receiving any medication and, except for obesity, there were no remarkable findings from their physical examination. Body composition was measured using bioimpedancemetry (Bioscan 920, Maltron International, Rayleigh, Essex). The anthropometric characteristics of the three groups of subjects are shown in **Table 1**. Each subject gave her written informed consent to the study after being informed of its nature, purpose, and potential risks, both verbally and in writing. The protocol was approved by the ethical committee of Lausanne University Faculty of Biology and Medicine.

Experimental protocol

At inclusion, the weights and heights of the subjects were measured, body composition was assessed, and resting energy expenditure was determined by indirect calorimetry during 60 min in the fasting state. The subjects were then instructed to follow a standardized isocaloric diet (50% carbohydrate, 35% fat, and 15% protein), and to avoid vigorous physical activity and caffeine- and alcohol-containing drinks the day before the test. The experiments began in the morning after a 10-h overnight fast. Upon arrival at the metabolic investigation unit, the subjects were asked to empty their bladders. Urine was collected at the end of the experiment to determine urinary nitrogen excretion rates. For collecting arterialized venous blood, a retrograde catheter was inserted in a vein in the dorsum of the hand, warmed in a thermostabilized box heated to 50 °C. Another catheter was inserted in a forearm vein of the contralateral arm for infusing 6,6 $^2H_2$ glucose. After a 2-h period to allow for tracer equilibration, an oral U ^{13}C-labeled glucose load was administrated (0.5 g/kg body weight, 2% enriched with ^{13}C glucose). Time 0 was taken as the time immediately preceding the glucose ingestion. After the ingestion and over a time period of 4 h, the rate of the 6,6 $^2H_2$ glucose infusion was adjusted to the expected rate of glucose appearance (20 μg/kg/min during the first 2 h, followed by rates of 30, 40, 30, and 20 μg/kg/min during each 60-min period thereafter).

Blood samples were collected at time points −120, −30, and 0 min for determining basal glucose production and basal hormone (insulin, ghrelin, polypeptide YY (PYY), gastric inhibitory polypeptide (GIP), glucagon-like peptide-1 (GLP-1)) and concentrations of substrates (glycemia, free fatty acids (FFA), etc.), and then at time points 15, 30, 45, 60, 90, and every 30 min so as to determine plasma glucose isotopic enrichments and concentrations of hormones and substrates. The samples were immediately centrifuged at 4 °C. Plasma was collected and stored at −20 °C until analysis. Respiratory gas exchanges were continuously monitored by open circuit indirect calorimetry (Datex, France).

Analytical procedures

Immediately after blood was drawn, plasma was separated by centrifugation at 4 °C for 10 min at 3,600 r.p.m. and stored at −20 °C. Plasma glucose was measured by the glucose oxydase method, using a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). Plasma concentrations of insulin, total ghrelin, total GLP-1, and total human PYY were determined by radioimmunoassay using specific kits (Linco Research, St. Charles, MO). Total GIP was determined by an enzyme-linked immunosorbent assay on unextracted plasma, using a specific kit from Linco Research (St. Charles, MO). FFA concentrations were analyzed using an enzymatic and colorimetric method (kit from Wako Chemicals, Neuss, Germany). Plasma 6,6 $^2H_2$ glucose and plasma U ^{13}C glucose isotopic enrichments were measured using gas chromatography mass spectrometry (GC 5890/MS5971; Hewlett-Packard, Palo Alto, CA), as previously described (19).

Calculations

The rate of glucose appearance (GRa) and the rate of glucose disappearance (GRd) were calculated from plasma 6,6 $^2H_2$ glucose enrichments according to Steele's equation for non-steady state, using a pool fraction of 0.75 and a distribution volume of 0.2 l/kg (20–22). The rate of EGA was calculated from plasma U ^{13}C enrichments using the method of Steele *et al.* (23). Hepatic glucose output was calculated as the difference between total glucose appearance and EGA.

Net glucose oxidation rates were estimated from gas exchange measurements, using the equations of Livesey and Elia (24,25). The net oxidation rate obtained corresponds to oxidation of endogenous glycogen in the fasting condition, and to oxidation of both endogenous glycogen and exogenous glucose after ingestion of glucose.

Statistical analysis

All data in the text, tables, and figures are expressed as mean values ± s.e.m. The areas under the curve were calculated using trapezoidal rules. Inter-group comparisons were made using ANOVA, corrected for multiple comparisons with post-hoc group comparisons using the Fisher test. We used the non-parametric test of Kruskal–Wallis for data that did not follow normal distribution. A P value <0.05 was considered to be statistically significant.

RESULTS

Characteristics of study groups

Table 1 shows the characteristics of the subjects of each of the three groups. There were no significant differences in age, weight, BMI, and body composition between the three groups at inclusion, but preoperative weight and BMI, and postoperative weight loss were higher in patients who had undergone RYGBP. All the subjects had been maintaining a stable weight for at least 3 months and were tested under the same conditions. Subjects who had undergone a GB procedure had a longer time interval between surgery and testing as compared to subjects who had undergone RYGBP (P < 0.05), because the former procedure has not been performed in our institution since April 2005.

Table 1 Subjects characteristics

	Control ($n = 8$)	RYGBP ($n = 8$)	GB ($n = 6$)	P
Age (years)	34.4 ± 3.8	34.0 ± 3.5	39.0 ± 3.0	NS
No. of months postoperative		26.7 ± 5.0	57.5 ± 9.1	0.014
Preoperative BMI		44.9 ± 1.8	41.1 ± 0.5	0.015
Postoperative weight loss		47.8 ± 3.3	32.4 ± 2.0	<0.01
Postoperative weight (kg)	79.3 ± 3.0	73.0 ± 6.4	76.4 ± 2.4	NS
Postoperative BMI (kg/m²)	29.2 ± 0.8	27.1 ± 1.5	28.9 ± 0.8	NS
Free fat mass (%)	64.8 ± 3.2	70.3 ± 2.6	62.3 ± 0.7	NS
Fat mass (%)	35.2 ± 3.2	29.7 ± 2.6	37.7 ± 0.7	NS

Glucose, insulin and FFA

Fasting glucose concentrations showed similar values in the three groups (RYGBP: 4.5 ± 0.2 mmol/l, GB: 4.7 ± 0.1 mmol/l, C: 5.0 ± 0.2 mmol/l; P = NS). As shown in **Figure 1a**, after the oral glucose load, there was a significantly earlier ($P < 0.01$) and exaggerated ($P = 0.0001$) rise in blood glucose in the RYGBP group as compared to the two other groups, with peak glycemia occurring at 45 min. Plasma glucose also returned to baseline significantly earlier in this group ($P = 0.0001$). Incremental areas under the curve (AUC) (RYGBP: 279.8 ± 44.0 mmol/l/min, GB: 348.0 ± 14.5 mmol/l/min, C: 336.6 ± 37.7 mmol/l/min, P = NS) were not significantly different among the three groups.

Patients who had undergone bariatric surgery (either RYGBP and GB) had significantly lower fasting insulin levels as compared to C participants (RYGBP: 45.8 ± 4.2 pmol/l, GB: 50.1 ± 4.6 pmol/l, C: 86.2 ± 14.3 pmol/l; C vs. RYGBP: $P < 0.05$; C vs. GB: $P < 0.05$). The RYGBP group exhibited an earlier and higher peak insulin response ($P < 0.01$) with a more rapid return to baseline as compared to the other two groups (**Figure 1b**). Total insulin secretion in response to the oral glucose load, as assessed by incremental AUC, was lower in the two bariatric surgery groups (RYGBP: 29,330.4 ± 3,568.8 pmol min/l, GB: 28,863.0 ± 6,736.3 pmol min/l, C: 43,426.1 ± 5,387.5 pmol min/l; RYGBP vs. C: $P < 0.05$; GB vs. C: $P = 0.051$). No significant difference was observed among the three groups as regards the fasting FFA (RYGBP: 672 ± 73 µmol/l, GB: 668 ± 54 µmol/l, C: 638 ± 48 µmol/l; P = NS). FFA concentrations after the meal were a mirror image of the glucose and insulin excursions; FFA showed an earlier decrease after the glucose ingestion in the RYGBP patients (**Figure 1c**).

Glucose kinetics

The time course of U ^{13}C-labeled glucose appearance (**Figure 2a**) paralleled the plasma glucose curve and accounted for the glycemic excursion. In the RYGBP group, EGA in the systemic circulation was accelerated ($P < 0.005$), consistent with more rapid absorption of the glucose meal by participants in this group. In addition, U ^{13}C-labeled glucose returned to baseline more rapidly in this group, indicating a more rapid disposition

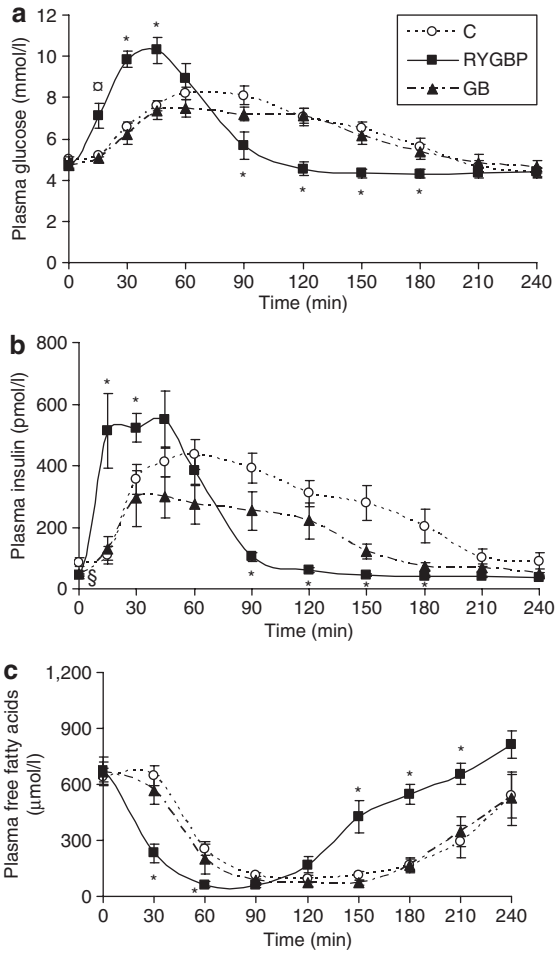

Figure 1 Time course of (**a**) plasma glucose, (**b**) insulin, and (**c**) free fatty acids. *$P \leq 0.05$, RYGBP vs. GB and C. ¤$P \leq 0.05$, RYGBP vs. C; §$P \leq 0.05$, RYGBP and GB vs. C. GB, gastric banding; RYGBP, Roux-en-Y gastric bypass.

of ingested glucose. However, no difference was observed among the three groups in the total EGA over the 4 h following the ingestion, as assessed by total AUC of EGA (RYGBP: 392.8 ± 12.3 mg/kg, GB: 367.3 ± 13.6 mg/kg, C: 383.1 ± 19.4 mg/kg; P = NS), thereby indicating similar absorption efficiencies of the glucose meal in all the groups. This represented 78.5% of the glucose load in the RYGBP group, 73.5% in the GB group, and 76.6% in the C group.

Hepatic glucose output (**Figure 2b**) was promptly inhibited after the ingestion of glucose in the three groups. This inhibition occurred earlier ($P < 0.05$) but was shorter-lived in the RYGBP group as compared to the other two groups. Basal levels of (Gra) and GRd were similar in the three groups (RYGBP: 1.9 ± 0.3 mg/kg/min, GB: 1.6 ± 0.2 mg/kg/min, C: 1.4 ± 0.2 mg/kg/min; P = NS for GRa and RYGBP: 1.9 ± 0.3 mg/kg/min, GB: 1.7 ± 0.3 mg/kg/min, C: 1.3 ± 0.1 mg/kg/min; P = NS for Grd). Total glucose appearance was predominant in the first 60 min in the RYGBP group (**Figure 2c**), but was the same in the three groups during the 4 h following the ingestion (RYGBP: 203.8 ± 22.8 mg/kg, GB: 137.8 ± 34.1 mg/kg, C: 181.5 ± 29.9 mg/kg; P = NS). The GRd (**Figure 2c**)

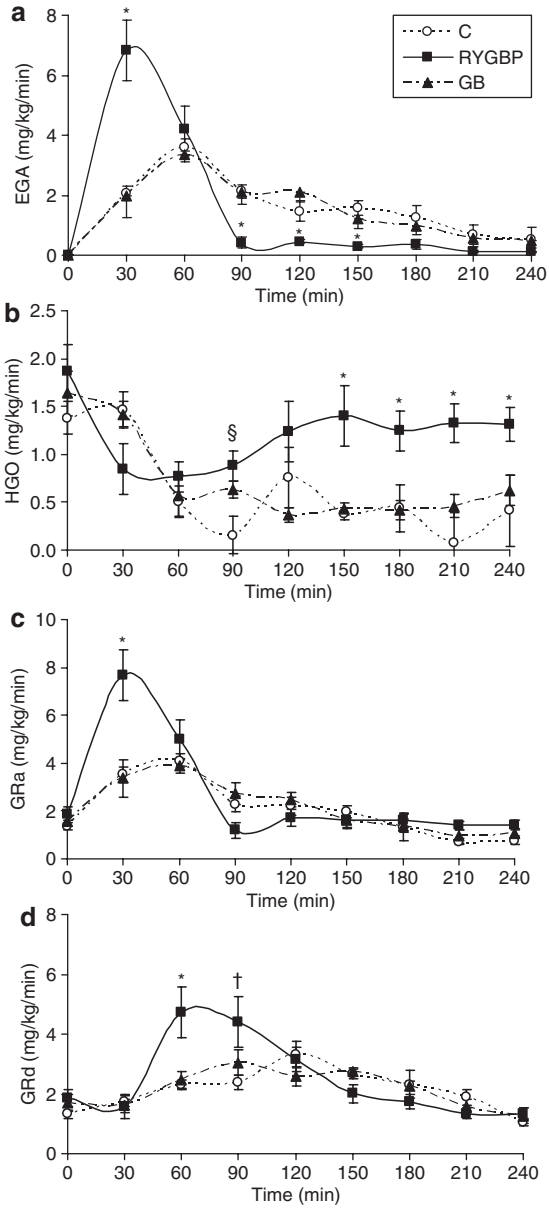

Figure 2 Time course of (**a**) exogenous glucose appearance (EGA), (**b**) hepatic glucose output (HGO), (**c**) glucose rate of appearance (GRa) and (**d**) glucose rate of disappearance (GRd). *$P \leq 0.05$, RYGBP vs. GB and C; §$P \leq 0.05$, RYGBP and GB vs. C; †$P \leq 0.05$, RYGBP vs. GB. GB, gastric banding; RYGBP, Roux-en-Y gastric bypass.

showed an increase and return to baseline earlier after the glucose ingestion in the RYGBP patients, but glucose disappearance during the 4 h was similar in the three groups (RYGBP: 214.8 ± 28.2 mg/kg, GB: 119.5 ± 48.7 mg/kg, C: 209.2 ± 32.6 mg/kg; P = NS). Fasting glucose clearance, as assessed by GRd divided by glucose concentration (GRd/glucose) was significantly different between RYGBP and C (RYGBP: 0.39 ± 0.03 mg/kg/min/mmol/l, GB: 0.36 ± 0.06 mg/kg/min/mmol/l, C: 0.27 ± 0.03 mg/kg/min/mmol/l; RYGBP vs. C: $P < 0.05$).

Energy expenditure and substrate oxidation

There was no significant difference among the three groups in either basal energy expenditure integrated from −60 to 0 min

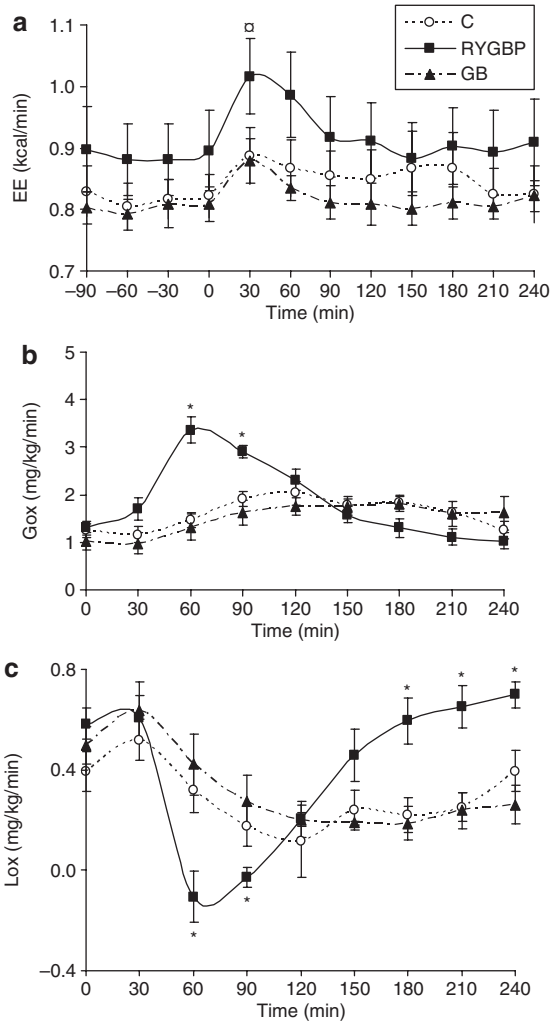

Figure 3 Time course of (**a**) energy expenditure (EE), (**b**) glucose oxidation (Gox) and (**c**) lipid oxidation (Lox). °$P \leq 0.05$, RYGBP vs. GB; $P \leq 0.05$, RYGBP vs. GB and C. GB, gastric banding; RYGBP, Roux-en-Y gastric bypass.

(RYGBP: 53.1 ± 3.6 kcal/min, GB: 48.3 ± 1.9 kcal/min, C: 48.9 ± 2.0 kcal/min; P = NS) or postprandial energy expenditure integrated from 30 to 240 min (RYGBP: 192.0 ± 13.6 kcal/min, GB: 170.5 ± 6.8 kcal/min, C: 176.3 ± 10.29 kcal/min, P = NS) (**Figure 3a**). **Figure 3b,c** show the glucose oxidation (Gox) and lipid oxidation (Lox) rates respectively, in the three groups of subjects. In the RYGBP group the glucose oxidation rate increased significantly at an earlier time point than in the other two groups, but net glucose oxidation over the course of the study was approximately equal in the three groups (RYGBP: 349 ± 73 mg/kg, GB: 321 ± 54 mg/kg, C: 390 ± 23 mg/kg, P = NS). In consonance with the changes in Gox rates, Lox showed an earlier decrease after glucose ingestion in the case of the RYGBP group.

Gut hormone secretion

There was no significant difference among the three groups in fasting ghrelin levels (RYGBP: 274 ± 76 pmol/l vs. GB: 430 ± 119 pmol/l and C: 343 ± 54 pmol/l, P = NS). In response to

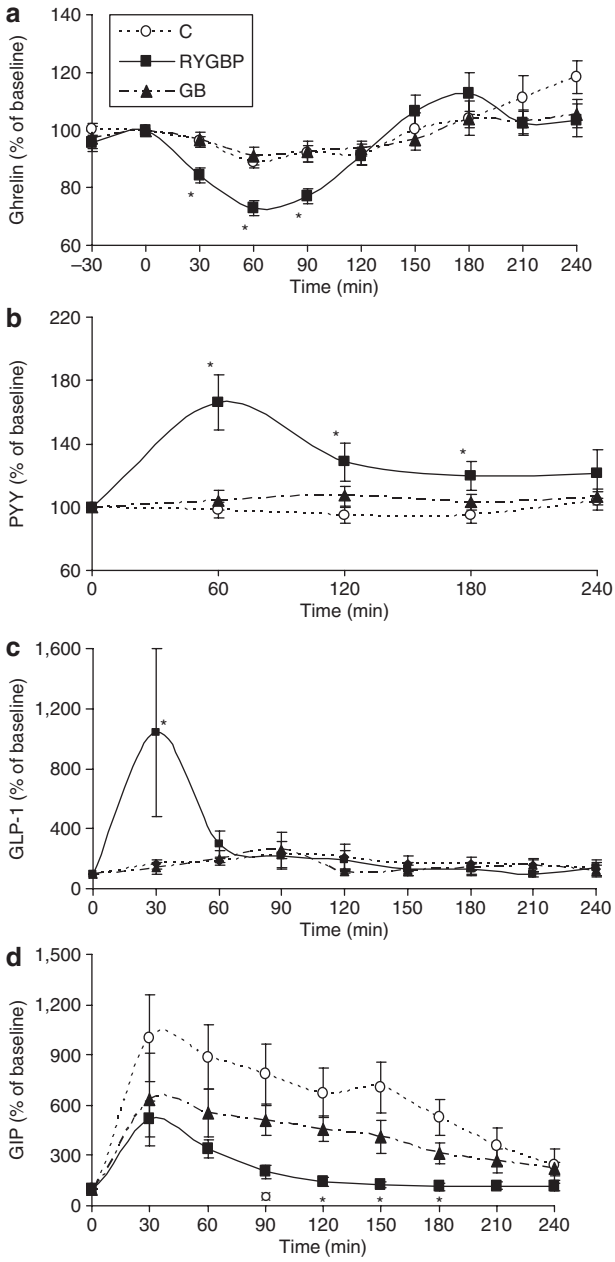

Figure 4 Time course of (**a**) plasma ghrelin, (**b**) polypeptide YY (PYY), (**c**) glucagon-like peptide-1 (GLP-1), and (**d**) gastric inhibitory polypeptide (GIP), expressed as a percentage of the initial value. *$P \leq 0.05$, RYGBP vs. GB and C; °$P \leq 0.05$, RYGBP vs. C. GB, gastric banding; RYGBP, Roux-en-Y gastric bypass.

the oral glucose load, ghrelin levels fell in all groups reaching a nadir at 60 min (Figure 4a). The maximal postprandial suppression was significantly greater in the RYGBP group than in the the GB and C groups (−27.2% vs. −11.4 and −14.8% respectively; $P < 0.0005$). Fasting PYY was higher in the RYGBP subjects (RYGBP: 37 ± 5 pmol/l vs. GB: 23 ± 2 pmol/l and C: 25 ± 2 pmol/l, RYGBP vs. C: $P < 0.05$), and the integrated PYY response to the oral glucose load was significantly enhanced in the RYGBP group as compared to the C and GB groups (RYGBP: 3,220 ± 1,243 pmol/l/min, GB: 201 ± 179 pmol/l/min, C: −243 ± 252 pmol/l/min; RYGBP vs. GB: $P < 0.05$, RYGBP vs. C: $P < 0.05$) (Figure 4b). There was no significant difference among the three groups in fasting GLP-1 levels (RYGBP: 7.9 ± 1.9 pmol/l vs. GB: 9.2 ± 2.3 pmol/l and C: 8.7 ± 2.8 pmol/l; P = NS). Patients with RYGBP had an exaggerated GLP-1 response to the oral glucose load (Figure 4c). The increase was >1,000% after 30 min in the RYGBP group, as compared to 138 and 162%, respectively, for the GB and C groups ($P < 0.005$). Postprandial GLP-1 secretion, as assessed by incremental AUC, was not significantly different among the three groups, but showed a trend toward an increase in the RYGBP group (RYGBP: 2,585 ± 489 pmol/l/min vs. GB: 1,203 ± 282 pmol/l/min and C: 1,261 ± 282 pmol/l/min, RYGBP vs. GB: $P = 0.062$, RYGBP vs. C: $P = 0.060$). Fasting GIP levels were similar in the three groups (RYGBP: 39.9 ± 10.6 pmol/l vs. GB: 25.8 ± 7.8 pmol/l and C: 21.5 ± 5.8 pmol/l; P = NS). After oral glucose ingestion GIP increased in the three groups, with a peak after 30 min (Figure 4d). The maximal concentration was not statistically different among the three groups (RYGBP: 163 ± 23.4 pmol/l vs. GB: 133.4 ± 11.1 pmol/l and C: 167.1 ± 28.7 pmol/l; P = NS). But the GIP postprandial response was short-lived ($P < 0.0001$) and total postprandial GIP secretion over the 4 h following the ingestion, as assessed by incremental AUC, was significantly reduced in the RYGBP group (RYGBP: 3,083.3 ± 1,258.7 pmol/ml/min, GB: 13,641.5 ± 799.4 pmol/ml/min, C: 18,374.5 ± 2,716.3 pmol/ml/min; RYGBP vs. C: $P < 0.05$).

DISCUSSION

A number of studies have reported an impressive and early improvement in glucose homeostasis in obese diabetes patients after bariatric surgery (4–13), but the mechanisms remain controversial. The primary aim of our study was to document the consequences of gastric surgery on postprandial glucose kinetics. Our results indicate that the rate of exogenous glucose absorption into the systemic circulation is markedly increased after RYGBP. This is reflected in the more rapid appearance of the tracer (added to the glucose meal) into the systemic circulation, and in the rapid postprandial rise in glycemia. This finding most likely reflects a rapid emptying rate from the gastric remnant. Although, to our knowledge, the rate of the emptying of nutrients from the gastric pouch has not been specifically assessed after RYGBP, there is ample evidence that it is accelerated after gastrectomy with Roux-en-Y loops in treating for cancer and gastric ulcers (26). We observed no episode of hypoglycemia amongst participants in this study. Such rapid delivery into the foregut may nonetheless play a role in the development of postprandial hypoglycemia or dumping syndromes in susceptible individuals (27–29).

As a result of the early rise in glycemia, plasma insulin concentrations increased earlier and reached much higher values in the RYGBP group than in the GB and C groups. In conjunction with this brisk insulin secretion, total glucose utilization was stimulated both earlier and to a greater extent, while suppression of endogenous glucose production was more rapid, but shorter-lived in the RYGBP group. In addition, the hyperglycemia observed in the RYGBP group may further stimulate

glucose utilization through an enhanced glucose-mediated glucose disposal.

The proportion of exogenous glucose appearing in the systemic circulation during the 4 h following the ingestion was similar in the RYGBP, GB, and C groups. Approximately 75% of the oral load was found in the systemic circulation in each group, with the remaining 25% probably accounted for by first-pass splanchnic glucose uptake (30). On the basis of these results it seems unlikely that there is significant glucose malabsorption following RYGBP.

The two surgical procedures appear to affect the glucose–insulin relationship significantly, although in different ways. RYGBP was shown to result in rapid increases in plasma insulin and glucose concentrations, followed by a rapid decrease and return to baseline values. When compared to the C group, the 4-h AUC for glucose was not altered in the RYGBP group, but AUC for insulin was lower. In contrast, in subjects who had undergone GB, the increase in plasma insulin showed the same time course as in the C group, but the increase was of a lower magnitude. This lower insulin response occurred in spite of an EGA rate and plasma glucose concentration values similar to those observed in C. Interestingly, the overall postprandial rise in plasma insulin, assessed as the incremental insulin AUC, tended to be reduced in the two bariatric surgery groups. Given that insulin AUC reflects insulin secretion, this suggests that the insulin requirement per unit of glucose ingested or appearing into the systemic circulation decreased after both RYGBP and GB. Our results may therefore indicate enhanced insulin sensitivity after bariatric surgery, but they do not indicate a differential effect for RYGBP vs. GB. However, the time courses of the plasma glycemic and insulin responses suggest that the mechanisms responsible for the lower insulin requirement are likely to be different post-GB and post-RYGBP. Future studies are required for quantitative evaluation of insulin sensitivity in such patients.

A major consequence of RYGBP is to divert nutrients away from the duodenum and deliver them directly to the more distal small bowel and the colon. This has important consequences for gastro-intestinal hormone secretion, which may be directly relevant to glucose homeostasis. An enhancement of the GLP-1 response was observed, and has already been reported in previous studies of patients with RYGBP (12,31–33) and in rats after RYGBP or ileal transposition (34,35). Early stimulation of GLP-1–secreting L-cells, located in the distal small bowel and colon, is most probably responsible for this effect. The increased levels of PYY secreted from L-cells (36) have also been reported in several other studies (31,33,37), thereby adding further support for arriving at this conclusion. On the other hand, we (and other researchers as well) (12,39) have observed that GIP, which is secreted by endocrine cells located in the proximal small bowel (40), reached lower levels postprandially and returned to basal concentrations more quickly in the RYGBP group of subjects.

It appears, therefore, that more direct delivery of nutrients to the distal small bowel favors early and enhanced secretion of GLP-1 after gastric bypass, and that this finding may be closely related to the effects of RYGBP on glucose homeostasis. One study, however, reported that RYGBP enhances GLP-1 secretion in patients with normal glucose tolerance and also in patients with impaired glucose tolerance, but not in patients with type 2 diabetes mellitus, although it improved glucose tolerance in all three groups (32). Another study failed to observe an increase in GLP-1 secretion after RYGBP, although glucose homeostasis improved after surgery (33). It is unclear why these two studies have thrown up conflicting results, but the cause may be related to differences in the assays used, differences in sample size, or the particular characteristics of the subjects. While the bulk of published information suggests that RYGBP causes increased postoperative secretion of GLP-1, there may be important variations among patients.

The effects of gastric surgery on ghrelin secretion are still poorly understood. It has been reported that RYGBP leads to a decrease in ghrelin levels early after surgery (18,33,41–44). However, since this initial observation, several reports have documented that basal ghrelin concentrations are only minimally affected several weeks/months after RYGBP (37,45–48). Our present observation further indicates that postprandial suppression of ghrelin was enhanced after RYGBP. Because ghrelin is produced mainly by cells located in the gastric fundus (49), this is consistent with the concept that the postprandial suppression of ghrelin secretion does not require the contact of food with the fundus of the stomach (50). It has been shown previously that plasma insulin is involved in the control of ghrelin secretion (51–56), and that plasma levels of ghrelin are reduced by insulin, possibly through the hypothalamus–stomach neural pathway (57). The higher postprandial suppression of ghrelin secretion after RYGBP could therefore be explained by the earlier and higher postprandial increase in plasma insulin level.

This study has some important limitations. First, it included only obese subjects who had no diabetes before surgery. The observations from the study, therefore, depict the effects of bariatric surgery *per se* on glucose kinetics and homeostasis. It nonetheless remains possible that some, yet unidentified, defects present in obese diabetes patients may be corrected by gastric surgery. Second, all studies were done following ingestion of a liquid glucose meal. It is therefore quite possible that different effects would have been observed after a solid mixed meal. This may be particularly true for gastric emptying in patients with GB. Third, postoperative weight loss, and the delay between surgery and the metabolic study, were different in patients who had undergone RYGBP and those who had undergone GB, and we cannot exclude the hypothesis that these factors impact on glucose homeostasis. Fourth, the study population was comprised exclusively of women; we assume these results will hold good for men as well, but that will require direct confirmation from future studies.

In summary, our present results indicate that RYGBP leads to marked changes in glucose kinetics after a liquid glucose meal, with an early appearance of exogenous glucose into the systemic circulation and a rapid clearance of glucose. The AUC for insulin was lowered in both RYGBP and GB patients after a glucose meal,

thereby suggesting that insulin requirements are decreased after these two procedures. Patients who had undergone RYGBP had increased postprandial PYY secretion and enhanced suppression of ghrelin, and this may contribute to reduce food intake. RYGBP leads to increased postprandial GLP-1 response, which may contribute to reduction in food intake and also to increase in postprandial insulin secretion, thereby playing a role in the restoration of glycemic control. These observations support the contention that a major part of the mechanism by which RYGBP causes weight loss and improvements in glucose metabolism is mediated by GI hormones.

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DISCLOSURE

The authors declared no conflict of interest.

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