Weight Loss, Appetite Suppression, and Changes in Fasting and Postprandial Ghrelin and Peptide-YY Levels After Roux-en-Y Gastric Bypass and Sleeve Gastrectomy

A Prospective, Double Blind Study

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Background: Bariatric surgery is currently the most effective treatment in morbidly obese patients, leading to durable weight loss.

Objective: In this prospective double blind study, we aim to evaluate and compare the effects of laparoscopic Roux-en-Y gastric bypass (LRYGBP) with laparoscopic sleeve gastrectomy (LSG) on body weight, appetite, fasting, and postprandial ghrelin and peptide-YY (PYY) levels.

Methods: After randomization, 16 patients were assigned to LRYGBP and 16 patients to LSG. Patients were reevaluated on the 1st, 3rd, 6th, and 12th postoperative month. Blood samples were collected after an overnight fast and in 6 patients in each group after a standard 420 kcal mixed meal.

Results: Body weight and body mass index (BMI) decreased markedly ($P < 0.0001$) and comparably after either procedure. Excess weight loss was greater after LSG at 6 months (55.5% ± 7.6% vs. 50.2% ± 6.5%, $P = 0.04$) and 12 months (69.7% ± 14.6% vs. 60.5% ± 10.7%, [$P = 0.05$]). After LRYGBP fasting ghrelin levels did not change significantly compared with baseline ($P = 0.19$) and did not decrease significantly after the test meal. On the other hand, LSG was followed by a marked reduction in fasting ghrelin levels ($P < 0.0001$) and a significant suppression after the meal. Fasting PYY levels increased after either surgical procedure ($P \leq 0.001$). Appetite decreased in both groups but to a greater extend after LSG.

Conclusion: PYY levels increased similarly after either procedure. The markedly reduced ghrelin levels in addition to increased PYY levels after LSG, are associated with greater appetite suppression and excess weight loss compared with LRYGBP.

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The epidemic of obesity is a major health problem in the developed world with a great influence on morbidity and mortality. Dietary and behavioral approaches to obesity have met with limited success and bariatric surgery is currently the only effective therapy for morbid obesity.[1] Benefits of surgery include durable weight loss, improved cardiovascular profile, remission of type II diabetes, and better quality of life.[2]

Laparoscopic Roux-en-Y gastric bypass (LRYGBP) has become very popular and has superseded any other kind of restrictive and malabsorptive operations.[3] LRYGBP results in greater weight loss compared with restrictive procedures in the absence of clinically significant malabsorption.[1] It seems to induce weight loss mainly through restriction of food intake and the dumping effect.[4] However, the exact mechanisms of weight loss are not well understood.

Laparoscopic sleeve gastrectomy (LSG) is a purely restrictive operation, initially applied to superobese patients with severe comorbidities as the first restrictive part of a mixed restrictive and malabsorptive operation, the biliopancreatic diversion-duodenal switch.[5] Recently, LSG has been applied as a sole bariatric operation in patients with body mass index (BMI) $\leq$50 kg/m^2.[6] Although early results on weight loss after LSG have been published,[7] the underlying mechanism of weight loss is still unknown and the long-term efficacy is under investigation.

Lately, it has been increasingly recognized that bariatric surgery has an effect on appetite and eating behavior. This may be relevant to changes after bariatric surgery in the circulating levels of gastrointestinal hormones known to influence appetite.[8] Ghrelin is the first identified peripheral orexigenic hormone. It is produced by cells scattered throughout the gastrointestinal tract but mainly by the oxyntic cells of the stomach.[9] Ghrelin injection stimulates food intake in rodents and humans via increased hypothalamic expression of the orexigenic neuropeptide Y.[10] Ghrelin has been proposed to have a role in meal initiation as the levels rise preprandially and fall proportionately in response to calorie ingestion.[11] Circulating ghrelin levels are decreased in human obesity.[12] In an initial study, ghrelin levels increased after diet induced weight loss, whereas weight loss after gastric bypass was associated with markedly suppressed ghrelin levels.[13] The

absence of the normal ghrelin adaptive response to weight loss after Roux-en-Y gastric bypass (RYGBP) could explain the decreased appetite observed in these patients. However, the above hypothesis has been challenged by recent studies that have shown conflicting data in postoperative plasma ghrelin levels after gastric bypass in morbidly obese patients.[14–18]

Peptide-YY (PYY) is a 36 amino acid peptide and a member PP fold peptide family. It is released postprandially from the distal gastrointestinal tract and it acts within the arcuate nucleus to inhibit the release of neuropeptide Y.[19] Intravenous infusion of $PYY_{3–36}$ in humans induces satiety and reduces food intake.[19,20] Recent studies have shown depressed PYY levels in morbidly obese individuals in comparison to lean controls[19–22] and blunted response in PYY release after meal stimulation.[22] Cross-sectional studies have demonstrated increased PYY levels and an exaggerated response to meal after RYGBP.[23,24]

The aim of this prospective double blind study was to evaluate and compare the effects of LRYGBP to the effects of LSG, a pure restrictive type of operation, on body weight, appetite and also on ghrelin and PYY levels.

PATIENTS AND METHODS

Human Studies

All human studies were performed according to the principles of the declaration of Helsinki. The study was approved by the research and ethics committee at the University Hospital of Patras. Exclusion criteria included chronic medical or psychiatric illness, substance abuse, and previous gastrointestinal surgery.

All patients were informed in detail about the risk and the benefits of each operation, and a written informed consent was obtained from all of them. Computer generated random numbers were used to assign the type of surgery (LRYGBP or LSG), which was written on a card sealed in a completely opaque envelop. All the operations were concluded laparoscopically and were performed by the same surgeon.

The LRYGBP technique included an antecolic-antegastric Roux-en-Y construction with a small gastric pouch (15–20 mL). The gastroenteroanastomosis was conducted with a 25-mm circular stapler and a 150-cm Roux limp was used.

In LSG, the vascular supply of the greater curvature of the stomach was divided from the left crus of the diaphragm to the pylorus. The dissection of the stomach began with a linear stapler commencing 3 cm from the pylorus, close to a 33 Fr bougie (introduced perorally by the anesthetist), up to the incisura angularis. A gastric sleeve tube of 40 to 60 mL in volume remained and 85% of the stomach was excised. Blinding as to the type of the procedure involved the patient and the medical stuff, and the independent data collector.

All subjects were admitted to the hospital the day before and at 1, 3, 6, and 12 months after the operation. All patients underwent complete evaluation during follow-up, including medications, nutritional behavior, anthropometric and clinical parameters, and blood sampling for glucose, triglycerides, cholesterol, and other laboratory tests. Venous blood for plasma ghrelin and PYY assays was collected after an overnight fast and in 6 patients in each group blood was also collected 2 hours after the consumption of a mixed 420 kcal meal (55% carbohydrate, 16% protein, and 29% fat). Weight loss evaluation was based on postoperative BMI and percent of excess weight loss (EWL%). Ideal body weight was determined according to the Metropolitan Life Insurance Company 1983 height/weight tables.

Hormone Assays

Blood was collected in ethylenediamine tetra-acetic acid-containing tubes for ghrelin and in heparin coated tubes containing 5000 kallikrein inhibitor units of aprotinin (Trasylol) for PYY. Samples were stored at 4°C during the short collection period, were centrifuged at 4°C and stored at −70°C until the assay. Serum ghrelin was measured in duplicate using a commercial radioimmunoassay (Phoenix Pharmaceuticals). It employs iodine 125-labeled bioactive ghrelin tracer and a rabbit polyclonal antibody against the full-length, octanoylated human ghrelin that recognizes the acylated and desacylated forms of the hormone. The lower limit of detection was 93 pg/mL, and the coefficient of intraassay variation was <8%. Serum PYY was measured in duplicate using a commercial radioimmunoassay (Phoenix Pharmaceuticals) containing iodine 125-labeled human PYY 3-36 and an antibody against human PYY 3-36 that exhibits 100% cross-reactivity with the full-length PYY. The lower limit of detection was 10 pg/mL and the coefficient of intraassay variation was <9%. All measurements were made in the same assay to reduce sources of variation.

Appetite Assessment

This study included also an interview focusing on appetite and based on visual analogue scales (VAS) that ranged from 0 to 100 mm. VAS was based on the Edmonton Symptom Assessment System VAS for appetite, which has been used extensively for the assessment of cancer induced cachexia and has been shown to be reliable.[25] The VAS consisted of 3 questions assessing food intake, appetite changes since the previous visit and hunger. To estimate satiety after meal consumption, the VAS question for hunger was repeated 2 hours later at the time of blood sample collection.

Statistical Analysis

Data are expressed as mean ± SD. Differences between means were evaluated using analysis of variance or the Student t test as appropriate. Differences were considered significant at $P < 0.05$.

RESULTS

After randomization, 16 patients underwent LRYGBP and 16 LSG. All procedures were successfully concluded laparoscopically with no conversion to open surgery. There were no intraoperative and postoperative complications. The 2 groups of patients had similar preoperative body weight and BMI, but the patients of the LSG group were younger ($P = 0.023$) (Table 1). Two patients of the LRYGBP group presented with diabetes mellitus and were on oral antidiabetic drugs, 1 with anemia, 5 with hypercholesterolemia, and 5 with hypertriglyceridemia. One patient in the LSG group had

TABLE 1. Patient Characteristics at Baseline

	N	Male/Female	Age (yr) (mean ± SD) (range)	Weight (kg) (mean ± SD) (range)	BMI (kg/m^2) (mean ± SD) (range)
RYGBP	16	4/12	37 ± 8.25 (21–55)	125.2 ± 14.7 (100–150)	46.6 ± 3.7 (40.2–51.9)
Sleeve gastrectomy	16	1/15	30.6 ± 7.8 (19–50)	122.1 ± 18.1 (96–160)	45.1 ± 3.6 (36.8–51.1)

TABLE 2. Hemoglobin Levels and Biochemical Parameters Before and 12 Months After Roux-en-Y Gastric Bypass and Sleeve Gastrectomy

	Preoperative (n = 16)			12 mo (n = 16)		
	LRYGBP	LSG	*P*	LRYGBP	LSG	*P*
Hb (g/dL)	13.4 ± 0.9	13 ± 0.9	0.3	14 ± 1.4	13 ± 1.5	0.06
Glucose (mg/dL)	98 ± 14	96 ± 12	0.62	89 ± 8	84 ± 8	0.1
Total cholesterol (mg/dL)	198 ± 36	177 ± 28	0.07	179 ± 35	176 ± 31	0.8
Triglycerides (mg/dL)	136.1 ± 84	111 ± 44	0.3	90 ± 27	74 ± 21	0.1
LDL (mg/dL)	134 ± 34	111 ± 23	0.03	111 ± 26	108 ± 23	0.7
HDL (mg/dL)	46.5 ± 9	43 ± 8	0.2	51 ± 10	53 ± 12	0.7
AST (IU/L)	21 ± 5	19 ± 5	0.28	23 ± 7	14 ± 3	<0.001
ALT (IU/L)	32 ± 19	27 ± 14	0.41	28 ± 8	13 ± 3	<0.001

glucose intolerance, 3 had anemia, 3 hypercholesterolemia, and 3 hypertriglyceridemia. The 2 diabetic patients in the LRYGBP group were excluded from the glucose analysis due to the very high preoperative glucose values (307 and 309 mg/dL, respectively). After excluding these 2 patients, mean glucose levels were similar in the 2 groups ($P = 0.62$). The LRYGBP group of patients had higher low-density lipoprotein (LDL) cholesterol and marginally higher total cholesterol levels (Table 2).

All patients had a complete evaluation at all time points of the follow-up. Either procedure was followed by a marked reduction in body weight and BMI $P < 0.001$) (Tables 3 and 4). The LRYGBP group lost 40.0 ± 8.3 kg 12 months after the operation and the LSG group 43.6 ± 11.7 kg ($P = 0.322$). The BMI at 12 months declined to 31.5 ± 3.4 kg/m^2 after LRYGBP and to 29 ± 3.6 kg/m^2 after LSG ($P = 0.41$). Excess weight loss was greater in the LSG group at 6 months ($P = 0.04$) and marginally greater at 12 months ($P = 0.05$) compared with LRYGBP group (Tables 3 and 4).

Both procedures were associated with a significant reduction in glucose levels (LRYGBP, $P = 0.03$; LSG, $P = 0.001$) (Table 2) and diabetes resolved in the 2 diabetic patients postoperatively. Fasting glucose levels were similar in the 2 groups of patients 12 months after the operation ($P = 0.1$). Triglyceride levels also decreased significantly in both groups postoperatively (LRYGBP, $P = 0.04$; LSG, $P = 0.01$) but the concentration was similar in both groups 12 months after surgery (Table 2). The decline in total and LDL choles-

TABLE 3. Body Mass Index, % Excess Weight Loss, Ghrelin, and PYY Changes Before and 1, 3, 6, and 12 Months After Roux-en-Y Gastric Bypass

	Pre (mean ± SD)	1 mo (mean ± SD)	3 mo (mean ± SD)	6 mo (mean ± SD)	12 mo (mean ± SD)	*P*
Body mass index (kg/m^2)	46.6 ± 3.7	41.9 ± 3.2	38.0 ± 3.1	34.3 ± 2.8	31.5 ± 3.4	<0.001
EWL%		20.5 ± 7.8	35.2 ± 5.4	50.2 ± 6.5	60.5 ± 10.7	<0.001
Fasting ghrelin (pg/mL)	638 ± 189	550 ± 136	610 ± 188	636 ± 188	714 ± 230	0.19
Fasting PYY (pg/mL)	132 ± 38	165 ± 55	173 ± 51	223 ± 79	199 ± 55	<0.001

TABLE 4. Body Mass Index, % Excess Weight Loss, Ghrelin, and PYY Changes Before and 1, 3, 6, and 12 Months After Sleeve Gastrectomy

	Pre (mean ± SD)	1 mo (mean ± SD)	3 mo (mean ± SD)	6 mo (mean ± SD)	12 mo (mean ± SD)	*P*
Body mass index (kg/m^2)	45.1 ± 3.6	41 ± 3.5	36.8 ± 3.4	32 ± 2.9	28.9 ± 3.6	<0.001
EWL%		18.2 ± 6.0	36.7 ± 6.8	55.5 ± 7.6	69.7 ± 14.6	<0.001
Fasting ghrelin (pg/mL)	605 ± 185	364 ± 83	399 ± 135	398 ± 100	399 ± 97	<0.001
Fasting PYY (pg/mL)	124 ± 30	155 ± 57	139 ± 44	182 ± 44	204 d ± 91	0.001

terol levels was not statistically significant after either procedure (LRYGBP, $P = 0.1$; LSG, $P = 0.78$), and the levels were similar postoperatively in the 2 groups (Table 2). AST and ALT decreased after both procedures, but the decline was greater after LSG (AST, $P < 0.001$; ALT, $P < 0.001$). The impact on hemoglobin levels was not significant (LRYGBP, $P = 0.087$; LSG, $P = 0.74$) (Table 2).

Preoperative fasting ghrelin and PYY levels were similar in both groups ($P = 0.62$ and 0.52, respectively) (Tables 3 and 4). Postoperatively, fasting ghrelin concentrations did not change significantly in the LRYGBP group ($P = 0.19$) but decreased markedly in the LSG group ($P < 0.001$) (Tables 3 and 4). Fasting PYY levels increased significantly and progressively after surgery in both study groups (Tables 3 and 4).

Six patients in each group were studied before and 2 hours after the consumption of a mixed meal. Preoperatively, the decline in ghrelin levels and the increase in PYY levels were borderline in the LRYGBP group of patients ($P = 0.06$ and 0.07, respectively) and significant in the LSG ($P = 0.02$ and 0.01, respectively) (Figs. 1, 2). Postoperatively, at 12 months, in the LSG group ghrelin levels decreased by 21.3%

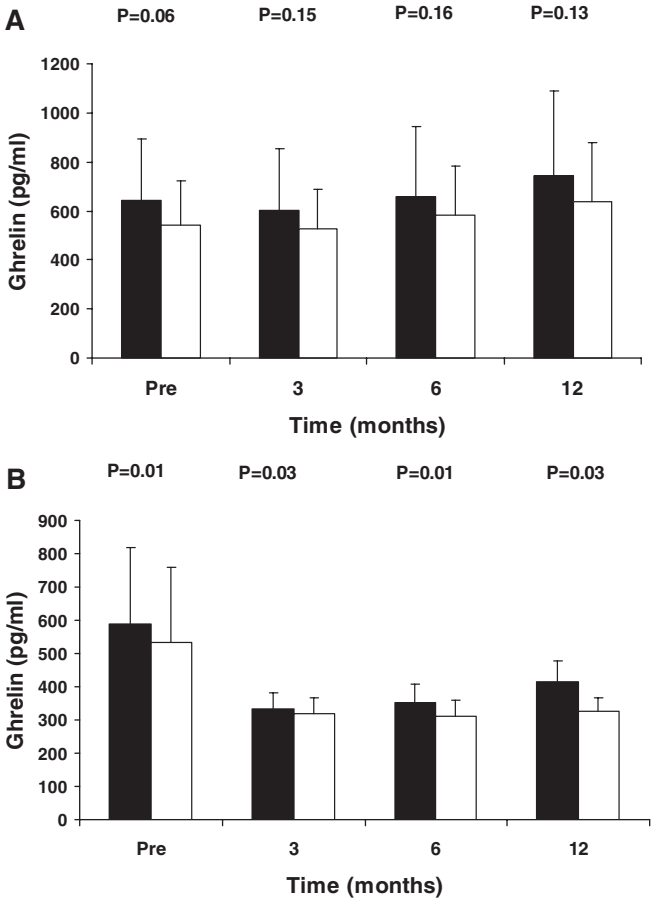

FIGURE 1. Meal induced changes in ghrelin levels in 6 patients after LRYGBP (A) and 6 patients after LSG (B). Fasting (black bar) and postprandial (white bar) ghrelin values. Error bars represent standard deviations.

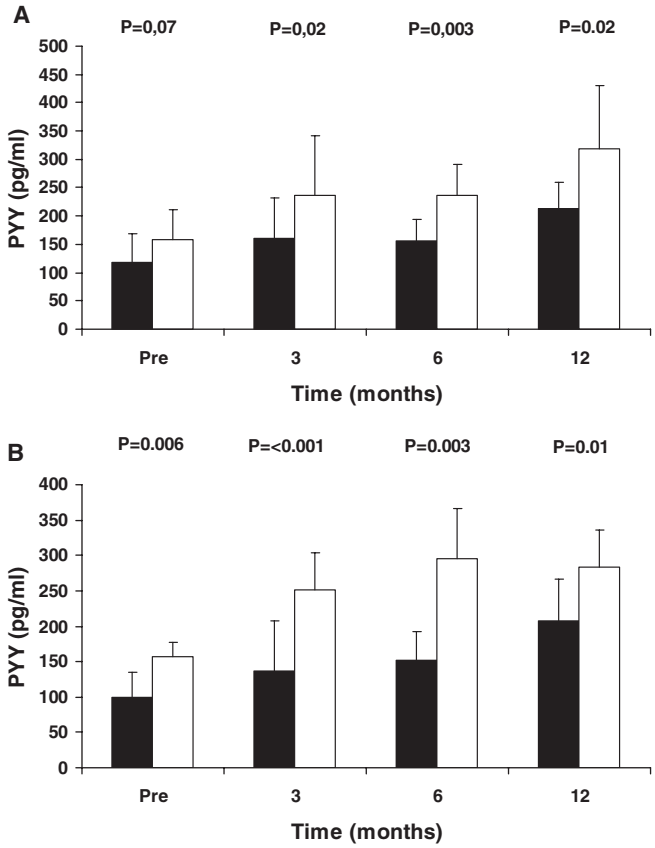

FIGURE 2. Meal induced changes in PYY levels in 6 patients after LRYGBP (A) and 6 patients after LSG (B). Fasting (black bar) and postprandial (white bar) PYY values. Error bars represent standard deviations.

($P = 0.03$) 2 hours after the meal compared with fasting levels, in contrast to the LRYGBP group where ghrelin suppression after the meal was 14% ($P = 0.133$) (Fig. 1). PYY levels 2 hours after meal increased significantly in both groups of patients compared with the fasting levels (Fig. 2).

Appetite assessment via VAS scores revealed a significant attenuation of appetite in both study groups (Fig. 3). Although food consumption remained at low levels in both study groups, patients subjected to LRYGBP demonstrated a gradual regain of appetite during the follow up. On the contrary, patients subjected to LSG had a greater appetite loss that was maintained during the whole study period.

DISCUSSION

In the present study, LRYGBP and LSG were associated with significant weight loss and appetite suppression but LSG was more effective in appetite suppression and excess weight loss. Both procedures resulted in similar increases in fasting and postprandial PYY levels but only LSG suppressed fasting and postprandial ghrelin levels significantly. The effect of LRYGBP on ghrelin levels was to abrogate the anticipated ghrelin increase after weight loss.

The weight loss after LRYGBP in the present study is in accordance with previous studies.[18,26] Gastric restriction

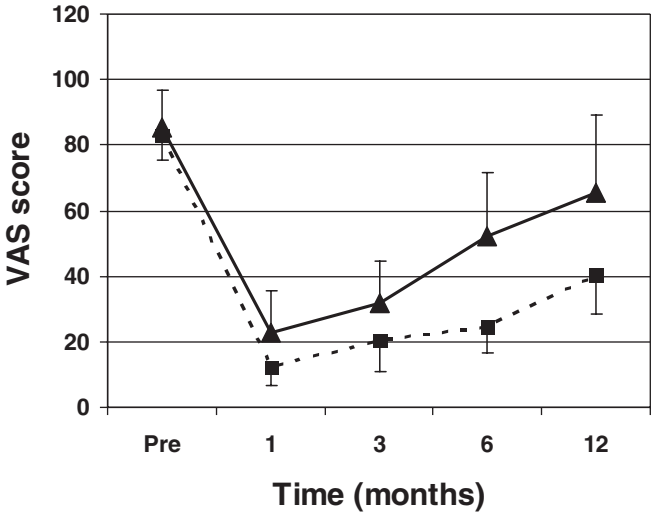

FIGURE 3. VAS recorded appetite changes after LRYGBP (--▲--) and LSG (--■--).

after LRYGBP plays an important role in weight loss as patients consume smaller meals and experience early satiety. It has been suggested that the greater efficiency of LRYGBP compared with other restrictive procedures is because of malabsorption and the dumping syndrome. However, clinically significant malabsorption is not observed after standard gastric bypass[27] and the dumping effect can contribute to weight loss only in sweet consumers.[28] Therefore, it is quite unlikely that these factors play a major role in weight loss.

Decreased appetite seems to play a dominant role in weight loss after gastric bypass. In a breakthrough study Cummings showed that weight loss after RYGBP was associated with a profound suppression of the orexigenic hormone ghrelin.[13] These findings were further supported by the study of Geloneze et al[29] in which fasting plasma ghrelin levels were significantly lower 1 year after RYGBP. However, subsequent prospective studies have shown inconsistent and conflicting ghrelin changes after gastric bypass.[30] In the present study, ghrelin levels did not change significantly after LRYGBP (Fig. 2), although a marked increase was anticipated because of weight loss.[13] A considerable number of additional studies have also reported no significant changes or even increases in postoperative ghrelin levels.[14–18,24] In a recently published study, we observed a 40% increase in ghrelin levels 1 year after biliopancreatic diversion-RYGBP, a surgical procedure that like LRYGBP involves exclusion of the gastric fundus.[31]

Differences in the surgical technique among centers, such as the size of the gastric pouch, the length of the Roux limp, and the handling of the vagus nerve have been proposed to account for these discrepancies in ghrelin postoperative data. The gastric pouch in our study was one of the smallest (20 ± 5 mL) and the biliopancreatic limb, although shorter than the 100 cm reported by Faraj et al,[15] was sufficiently long (50 cm) to preclude reflux of nutrients in the duodenum. Furthermore, in our common practice we take all the necessary precautions to avoid damage to the vagus nerve.

Borg et al,[24] in a recent study of 6 patients after RYGBP, reported no difference between preoperative and postoperative postprandial ghrelin levels. This agrees with our observation that a 420-kcal mixed meal did not suppressed significantly plasma ghrelin levels ($P = 0.13$) in patients subjected to LRYGBP. The weakness of our study is that instead of serial postprandial samplings a single sample was only recorded at 2 hours postmeal.

Obesity is associated with lower basal PYY levels[20–22,31] and a blunted response of PYY to meal stimulation compared with lean controls.[22] Fasting PYY levels increased significantly after LRYGBP in the present study (Table 3) and this is in agreement with previous reports.[23,24] Additionally, a significant response to a test meal was observed (Fig. 2). PYY induces satiety and the increased fasting and postprandial levels after LRYGBP have been proposed to account for the durable decreased appetite and weight loss.

Elevated levels of PYY have been observed in various gastrointestinal diseases, such as chronic pancreatitis, tropical sprue, Crohn's disease, and ulcerative colitis, which are associated with malabsorption due to abnormal delivery of undigested fat to the distal small bowel and decreased appetite.[32] PYY rise leads to delayed gastric emptying and mouth to cecum transit, the so-called "ileal brake mechanism." In these pathologic states, PYY increases as an adaptive response to increase the conduct time of the nutrient chyme with the decreased absorptive surface. Presumably, it is the same physiologic mechanism that governs PYY level rise after LRYGBP and can explain, at least in part, the observed anorectic state.

LSG is a purely restrictive procedure with no malabsorption arm. Presumably, mechanical restriction accounts for the decreased caloric intake leading to weight loss. In the present study, the patients subjected to sleeve gastrectomy had their stomach reduced to a narrow tube over the lesser curvature and the remaining 85% of it, including the fundus, was excised. In accordance to the literature reporting EWL% ranging from 33% to 83.3%,[8] we observed a EWL% of $69.7\% \pm 14.6\%$ at 12 months after LSG. Because of this quite favorable weight loss, LSG (although originally designed as an initial tool to an intended malabsorptive procedure) can serve as a sole bariatric procedure.

Because the gastric fundus is the main location of ghrelin-producing cells, one would expect the observed decreased plasma ghrelin levels after LSG (Table 4). Langer et al[33] and Cohen et al[34] reported the same findings in obese and super obese patients subjected to LSG. However, in both studies the ghrelin response to a meal intake was not examined. Interestingly, after a 420-kcal mixed meal, we observed a further 21.3% decrease in the already diminished ghrelin levels ($P = 0.03$).

LSG preserves the integrity of pylorus and does not include intestinal bypass as part of the technique. Therefore, it would be reasonable not expect any significant changes in PYY. However, we observed a significant increase both in fasting and postprandial PYY levels. It has been shown that intraduodenal infusion of lipids in humans leads to a rise in PYY levels before nutrients reach the distal Gastrointestinal

tract, suggesting the participation of neural or humoral mechanisms in modulation of PYY release.[35] LSG is associated with incomplete digestion due to decreased gastric acid secretion. Delivery to the duodenum of undigested chyme of higher pH could enhance PYY response to the meal.

In our series, the stimulatory meal effect on PYY gradually diminished from 94.4% increase at 6 months to 36.4% at 12 months. Himpens et al, in a recent study of 40 patients subjected to sleeve gastrectomy, reported a 21.8% incidence of gastro esophageal reflux disease at 12 months, which was significantly reduced to 3.1% at 3 years, suggesting an increased gastric compliance.[36] Based on these findings, we could speculate that PYY response to meal ingestion gradually decreases, due to physiologic adaptation of the gastric remnant leading to better digestion. If this hypothesis is correct, the long-term efficiency of LSG on appetite suppression and weight loss is under question and a further follow-up in depth of time is required.

In the present study, although appetite and food consumption were diminished after either procedure, a partial recovery of appetite was observed in the LRYGBP group at 12 months. On the contrary, patients subjected to LSG maintained a markedly reduced appetite throughout the study period. Because PYY levels were equally increased in both study groups, we can assume that the lower ghrelin levels after LSG account for the greater appetite suppression. A recently published animal study reported that ghrelin in a dose-dependent manner attenuates the anorectic effect of PYY and glucagon-like peptide 1.[37] This observation supports our hypothesis that the sustained ghrelin reduction acts additively to suppress appetite and explains the greater efficacy of LSG over RYGBP.

Both types of operations were associated with significant metabolic benefits. Diabetes resolved and glucose levels decreased postoperatively in both study groups as a result to the improvement of insulin resistance due to marked reduction in calorie intake, weight loss, and reduction in fat mass. Moreover, postoperative increased levels of gut hormones, such as glucagon-like peptide-1 that amplify β-cell response to nutrients, are also relevant as previously discussed.[38] Triglycerides decreased significantly after either procedure but the decrease in total and LDL cholesterol levels was not significant.

Nonalcoholic fatty liver disease represents a common entity in morbidly obese patients. We observed a significant decline in liver enzymes postoperatively in both groups and this is consistent with previous studies demonstrating favorable results after weight reducing operations.[38–40] No significant impact on hemoglobin levels was observed after either procedure during the 12-month follow-up.

In conclusion, the results of this study suggest that LSG is superior to LRYGBP in terms of EWL%. Durable weight loss after both procedures is partly because of volume restriction but also to the marked increase in fasting and postprandial PYY levels leading to increased satiety. LSG in addition to the above mechanisms decreases significantly fasting and postprandial ghrelin levels, which remain stable after LRYGBP. The marked suppression of ghrelin levels after LSG is associated with greater appetite reduction and excess weight loss during the first postoperative year.

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