

First-phase insulin secretion, insulin sensitivity, ghrelin, GLP-1, and PYY changes 72 h after sleeve gastrectomy in obese diabetic patients: the gastric hypothesis

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Abstract

Background The aim of this study was to evaluate the possible role of sleeve gastrectomy (SG) per se in the reversibility of diabetes.

Methods Insulin secretion and peripheral insulin sensitivity using the intravenous glucose tolerance test (IVGTT) were assessed in 18 obese type 2 diabetic patients and in 10 nondiabetic obese patients before and 3 days after SG, before any food intake and any weight change occurrence. At the same time, ghrelin, GLP-1, and PYY levels were determined.

Results In diabetic patients who had the disease less than 10.5 years, the first phase of insulin secretion promptly improved after SG. The early insulin area under the curve (AUC) significantly increased at the postoperative IVGTT, indicating an increased glucose-induced insulin secretion. The second phase of insulin secretion (late AUC) significantly decreased after SG in all groups, indicating an improved insulin peripheral sensitivity. In all groups, pre- and postoperatively, intravenous glucose stimulation determined a decrease in ghrelin values and an increase in GLP-1 and PYY values. However, in the group of patients with disease duration >10.5 years, the differences were not significant except for the late insulin AUC. Postoperative

basal and intravenous glucose-stimulated ghrelin levels were lower than preoperative levels in all groups of patients. Basal and intravenous stimulated GLP-1 and PYY postoperative values were higher than preoperative levels in all groups.

Conclusions Restoration of the first phase of insulin secretion and improved insulin sensitivity in diabetic obese patients immediately after SG, before any food passage through the gastrointestinal tract and before any weight loss, seem to be related to ghrelin, GLP-1, and PYY hormonal changes of possible gastric origin and was neither meal- nor weight-change-related. Duration of the disease up to 10.5 years seems to be a major cut off in the pathophysiological changes induced by SG. A “gastric” hypothesis may be put forward to explain the antidiabetes effect of SG.

Keywords Type 2 diabetes · Sleeve gastrectomy · Glucose metabolism · Metabolic surgery

Weight-loss surgery has been shown to reduce mortality and comorbidities and, most significantly, it seems to ameliorate or resolve type 2 diabetes mellitus (T2DM) [1]. Buchwald [2] reported that the antidiabetes effect of bariatric surgery was greatest in patients who underwent a biliopancreatic diversion/duodenal switch (95.1% of resolution) followed by a gastric bypass (80.3%), gastroplasty (79.7%), and then laparoscopic adjustable gastric banding (56.7%).

Sleeve gastrectomy (SG), originally conceived as the first stage of a biliopancreatic diversion with duodenal switch (BPD-DS) and recently proposed as potentially a single restrictive bariatric procedure, is associated with a high rate of resolution of T2DM and other

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obesity-associated comorbidities such as hypertension, hyperlipidemia, and sleep apnea [3–5].

Vidal et al. [6] reported that in the short term (4 months), SG and gastric bypass (GBP) have a similar impact on diabetes. A study performed in our center confirmed the early effect of SG on T2DM/Impaired Glucose Tolerance (IGT), with a resolution rate of 66.6% after 3.3 months [7]. Moreover, a marked and very early (3–5 days) reduction in Homeostasis Model of Assessment—Insulin Resistance (HOMA IR) in T2DM patients was observed after SG, thus indicating a rapid and remarkable improvement in insulin sensitivity unrelated to weight loss [8].

Salinari et al. [9] studied first-phase insulin secretion and insulin sensitivity in diabetic patients before and 1 month after BPD, demonstrating an improvement of both parameters.

Recently, Peterli et al. [10] analyzed the fasting and test meal-stimulated GLP-1, PYY, and ghrelin modifications after GBP and SG. A statistically significant reduction in fasting ghrelin concentrations was observed in both procedures. After a standard test meal, an early (1 week) significant increase in the GLP-1 and PYY area under the curve (AUC) and a significant decrease in the ghrelin AUC were reported in both procedures. The authors concluded rejecting the idea that the proximal small intestine mediates the improvement in glucose homeostasis after bariatric surgery.

The purpose of the present work was to evaluate the effect of SG on the glycemic profile, insulin secretion and sensitivity, and basal and intravenous glucose-stimulated ghrelin, GLP-1, and PYY levels immediately after SG before any food passage through the gastrointestinal tract and before any weight loss with the aim of ascertaining whether SG per se affects glucose metabolism and induces hormonal changes.

Materials and methods

Twenty four consecutive obese diabetic patients were considered for inclusion in the study. Six will be excluded because basal glucose values exceeded 200 mg/dl, which contraindicated the intravenous glucose tolerance test (IVGTT). Eighteen morbidly obese T2DM patients and ten normotolerant obese patients were studied. The diabetic patients were all characterized as having T2DM according to the American Diabetes Association (ADA) criteria. Twenty-four diabetic patients < were subdivided into two groups according to the length of time the patient had diabetes, using the statistical median as the value that separates the higher half of the sample from the lower half. The median value was 10.5 years. Group A comprised those patients who had the disease for less than 10.5 years (12 diabetic patients, 7 women and 5 men, age = 48.3 ± 9.1 years, BMI = 43.5 ± 6.6 kg/

m², HbA1c = $6.6 \pm 0.7\%$). Group B comprised those patients who had the disease for more than 10.5 years (12 diabetic patients, 8 women and 4 men, age = 54.5 ± 4.8 years, BMI = 38.6 ± 8.1 kg/m², HbA1c = $10.1 \pm 2.3\%$). Group C comprised 10 nondiabetic obese patients (6 women and 4 men, age = 43.0 ± 11.2 years, BMI = 45.1 ± 6.9 kg/m²).

In each group the presence of hypertension and dyslipidemia according to ATP III criteria and obstructive sleep apnea syndrome (OSAS) by polysomnography was assessed. In group A, hypertension and OSAS were present in 50% of patients (6/12) and dyslipidemia in 91.6% (11/12). In group B, hypertension was observed in 100% (6/6) of the patients, OSAS in 33.3% (2/6), and dyslipidemia in 66.6% (4/6). In group C, hypertension occurred in 60% (6/10) of the patients, OSAS in 40% (4/10), and dyslipidemia in 70% (7/10).

In all patients an IVGTT was performed before and after SG. Preoperatively, all patients underwent IVGTT after 3 days of starvation during which only 2.5 l of intravenous noncaloric liquids was administered in the absence of antidiabetes drugs. Electrolytic parameters, blood pressure, and cardiac frequency measurements were assessed twice daily. Plasma glucose was checked every 4 h; values over 200 mg/dl were considered cause for exclusion from the study. After 3 days, the patients ate normally for 3 days before SG. They again underwent IVGTT 3 days after surgery without receiving nutrients, caloric liquids, or antidiabetes drugs, in order to avoid weight changes and interference of intestinal mechanisms on insulin secretion and sensitivity and hormonal changes (Fig. 1). IVGTT was not performed in six diabetic patients because they had fasting glucose over 200 mg/dl before the test. Thus, group B was made up of 6 patients (4 women and 2 men).

In each group the total AUC for insulin during IVGTT before and after surgery was calculated in order to compare

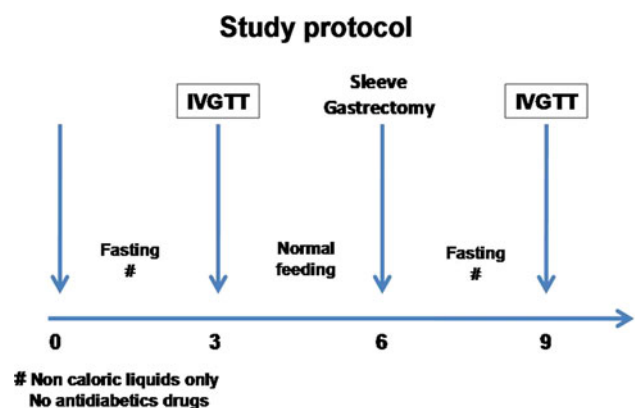


Fig. 1 Study protocol: IVGTT was performed before and after surgery with comparable conditions of fasting and antidiabetes treatment

changes in insulin secretion. Early insulin AUC and late insulin AUC were measured as an expression of first-phase insulin secretion and insulin sensitivity, respectively.

Ghrelin, GLP-1, and PYY levels were evaluated pre- and postoperatively before and 15 min after the intravenous bolus of glucose. Moreover, in all patients ghrelin and GLP-1 values were evaluated perioperatively, i.e., before pneumoperitoneum, at the end of the gastrectomy, and 6 and 24 h after surgery.

The study protocol was approved by the institutional ethics committee of the “Sapienza” University of Rome. The nature and purpose of the study were carefully explained to all subjects before they provided their written consent to participate.

IVGTT

An IVGTT was performed preoperatively and within 3 days postoperatively. Between 8:00 and 9:00 a.m., after 3 days of fasting before surgery and on the third postoperative day, an intravenous catheter was placed in an antecubital vein. An intravenous bolus of 12 g glucose/m² body surface as 50% water solution was injected. Blood samples for glucose and insulin were drawn from the contralateral antecubital vein at 0, 2, 3, 5, 10, 15, 20, 30, 40, 60, 90, 120, 180, and 240 min after glucose injection. Samples were placed in chilled tubes and plasma was separated within 20 min and stored at -20°C . Each blood sample was stored until the insulin, ghrelin, GLP-1, and PYY assays were performed.

Laparoscopic sleeve gastrectomy

SG was performed according to the technique described by Gagner [5]. The skeletization of the greater curvature of the stomach started at 6–8 cm from the pylorus and went up to the angle of His using a radiofrequency device. A 48-Fr transoral bougie was positioned from the hiatus to the duodenum along the lesser curvature. The SG was performed using a linear stapler (EndoGIA®, US Surgical, Norwalk, CT, USA), with sequential 4.8/60-mm green cartridge load firings for the antrum and 3.5/60-mm blue cartridge for corpus and fundus. A 60–80-ml gastric pouch was finally obtained.

Analytical procedures

Plasma glucose was measured by the glucose oxidase technique on a Beckman Glucose Analyzer (Beckman, Fullerton, CA, USA). Plasma insulin was assayed using an immunoradiometric assay (RADIM Diagnostic, Italy). Plasma ghrelin was measured using a commercially available RIA kit (Phoenix Pharmaceuticals Inc., Phoenix,

AZ, USA). GLP-1 was measured using a commercially available ELISA kit (Linco Research, St. Charles, MO, USA). These samples were collected in tubes containing DPP-IV inhibitor (Millipore, Billerica, MA, USA). PYY was measured using a commercially available kit (Phoenix Pharmaceuticals) containing ¹²⁵I-labeled human and an antibody against human 3–36 that exhibits 100% cross-reactivity with the full length.

Data are expressed as mean \pm SEM unless indicated otherwise. Descriptive statistics were used for demographic variables such as age, weight, height, and BMI. Hormones were analyzed by calculating time courses and AUC. Statistical analyses were performed using SPSS software ver. 15.0 (SPSS, Inc., Chicago, IL, USA). Statistical significance was set at $P < 0.05$.

Results

As expected, weight loss 3 days after SG was not significant (120.44 ± 25.4 vs. 120.03 ± 25.24 kg). In all groups of patients, basal plasma values of glucose and insulin before surgery were not significantly different from the postsurgery values. Insulin concentrations during IVGTT before and after surgery are shown in Fig. 2. AUCs for total, early, and late insulin were calculated in all three groups.

Group A

In group A, AUCs for total insulin before and after surgery were not significantly different. On the other hand, early insulin AUC showed a significant increase after surgery compared to preoperative values (from 133.50 ± 86.70 to $254.10 \pm 158.44 \mu\text{UI ml}^{-1}\text{ min}$; $P = 0.012$) (Fig. 3). As shown in Fig. 4, the late insulin AUC, as an expression of insulin sensitivity, showed a significant reduction after surgery compared to preoperative values (from $5,275.00 \pm 4,533.900$ to $3,552.41 \pm 3,326.32 \mu\text{UI ml}^{-1}\text{ min}$; $P = 0.04$). Basal ghrelin plasma concentrations decreased significantly after SG. During IVGTT, at 15 min ghrelin values diminished before and after SG. The postoperative IVGTT-stimulated ghrelin reduction was statistically significant when compared with the preoperative value (Fig. 5). After SG, basal GLP-1 values were significantly increased compared to the preoperative values. During pre- and postoperative IVGTT, intravenous glucose infusion induced an increase in GLP-1 values, although it was not statistically significant. However, postoperatively, 15 min after intravenous glucose stimulation, GLP-1 values were significantly increased compared to the preoperative values (Fig. 6). After SG, basal PYY values increased compared to the preoperative values but not significantly. Postoperative PYY values, 15 min after

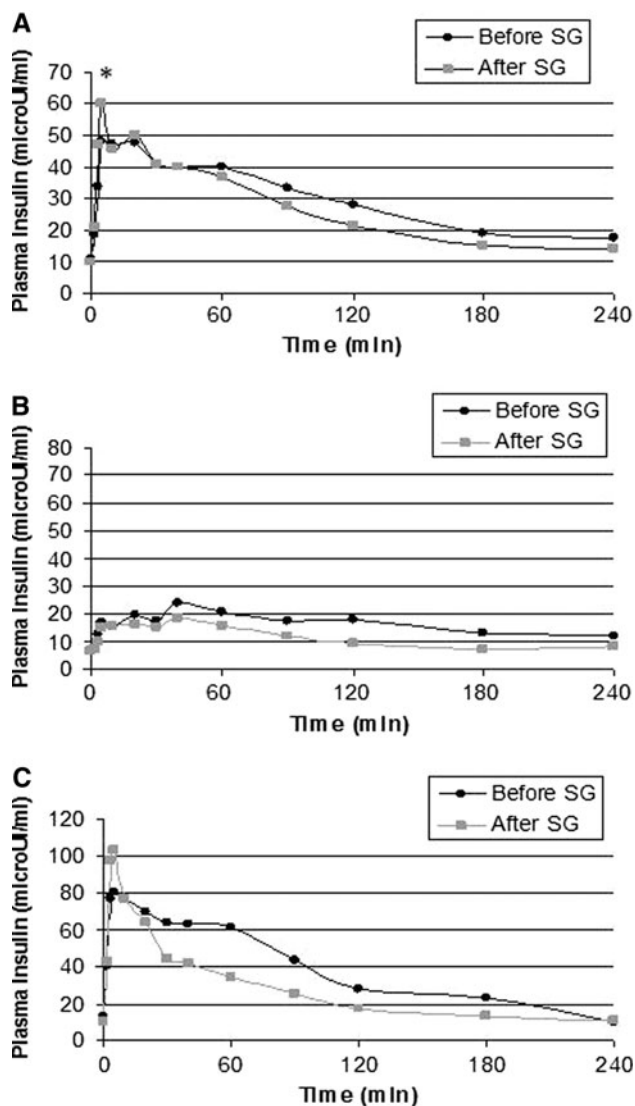


Fig. 2 Insulin values during IVGTT before and after surgery in group A (<10 years of disease duration), group B (>10 years), and group C (nondiabetic obese patients); * $P = 0.012$

intravenous glucose stimulation, were significantly increased compared to the preoperative values (Fig. 7).

Group B

During IVGTT, there were no differences among the AUCs for total and early insulin before and 3 days after surgery. All patients showed the absence of the first phase of glucose-induced insulin secretion before surgery, which did not recover after SG (Fig. 2). On the other hand, we observed the reduction of the AUC for late insulin as expression of an amelioration of insulin sensitivity (from $3,891.66 \pm 2,115.98$ to $1,825.33 \pm 988.83 \mu \text{UI ml}^{-1} \text{ min}$, $P = 0.045$) (Fig. 4). The modification in the ghrelin values observed in this group were similar to those in

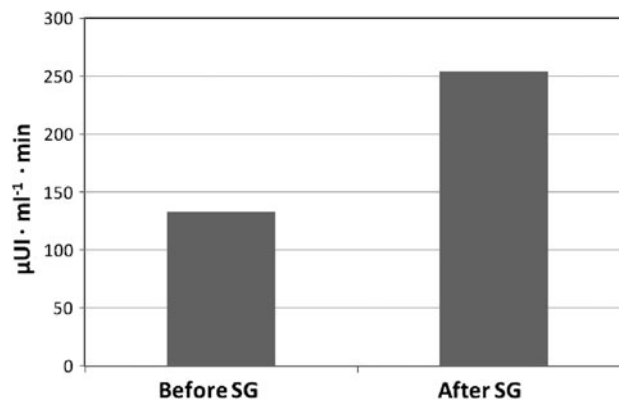


Fig. 3 Early insulin AUC in group A before and after SG; $P = 0.012$

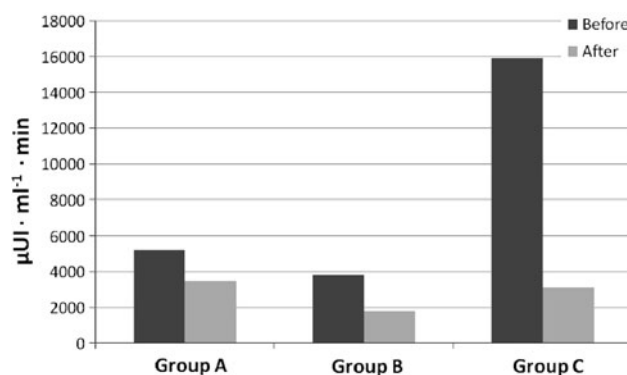


Fig. 4 Late insulin AUC before and after SG in group A ($P = 0.04$), group B ($P = 0.04$), and group C ($P = 0.028$)

group A (Fig. 5). As in group A, in patients with a history of diabetes for more than 10.5 years, GLP-1 values increased at 15 min during pre- and postoperative IVGTT. Postoperative basal and stimulated GLP-1 values were higher than the preoperative values; however, the differences were not statistically significant (Fig. 6). After SG, basal and stimulated PYY values increased, but not significantly, compared to the preoperative values (Fig. 7).

Group C

During IVGTT, there were no differences among the AUCs for total and early insulin before and 3 days after surgery. All patients showed a normal peak for the first phase of glucose-induced insulin secretion before and after surgery (Fig. 2). The late insulin AUC showed a significant reduction after surgery compared to the preoperative values (from $15,906.20 \pm 3,297.91$ to $3,156.40 \pm 2,532.68 \mu \text{UI ml}^{-1} \text{ min}$, $P = 0.028$) (Fig. 4). In this group, modifications to ghrelin values were similar to those of groups A and B (Fig. 5). During pre- and postoperative IVGTT, GLP-1

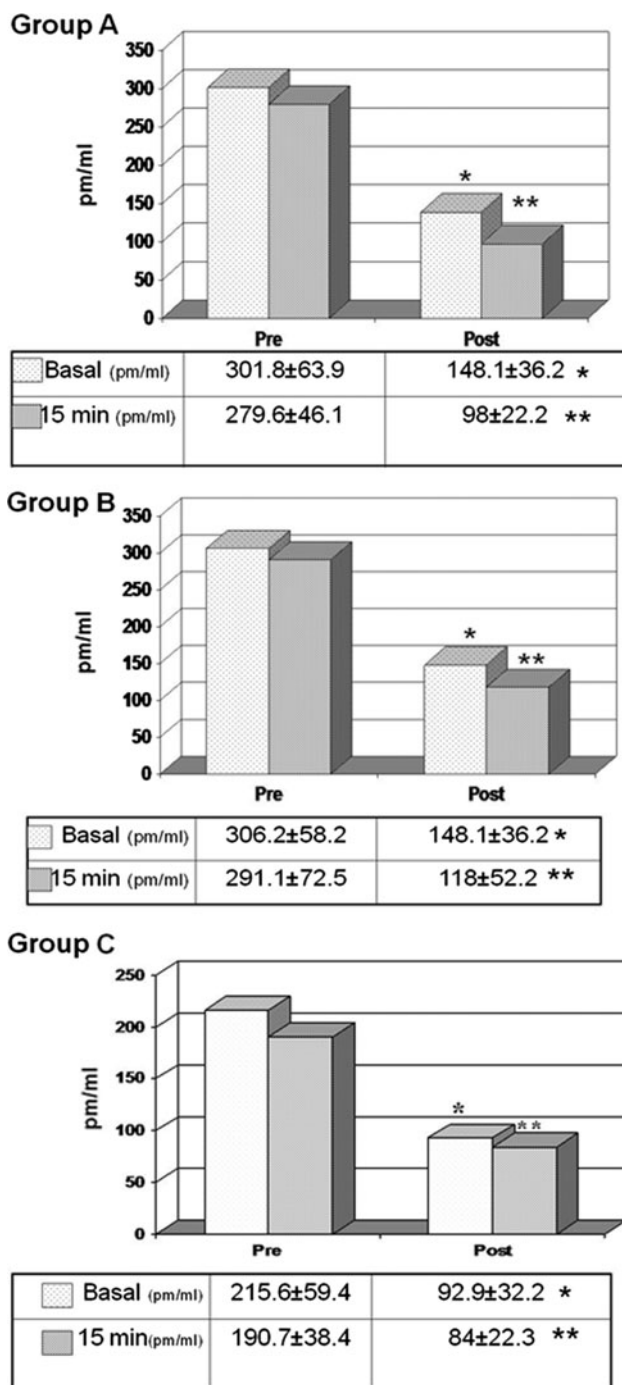


Fig. 5 Ghrelin values in basal conditions and at 15 min. During IVGTT before and after surgery in group A (<10 years of disease duration), group B (>10 years), and group C (nondiabetic obese patients); *,** $P < 0.005$ with preoperative values

values increased at 15 min. After SG, statistically significant increases in basal and stimulated plasma GLP1 concentrations were observed (Fig. 6). Basal and intravenous glucose-stimulated PYY plasma concentrations increased significantly after SG (Fig. 7).

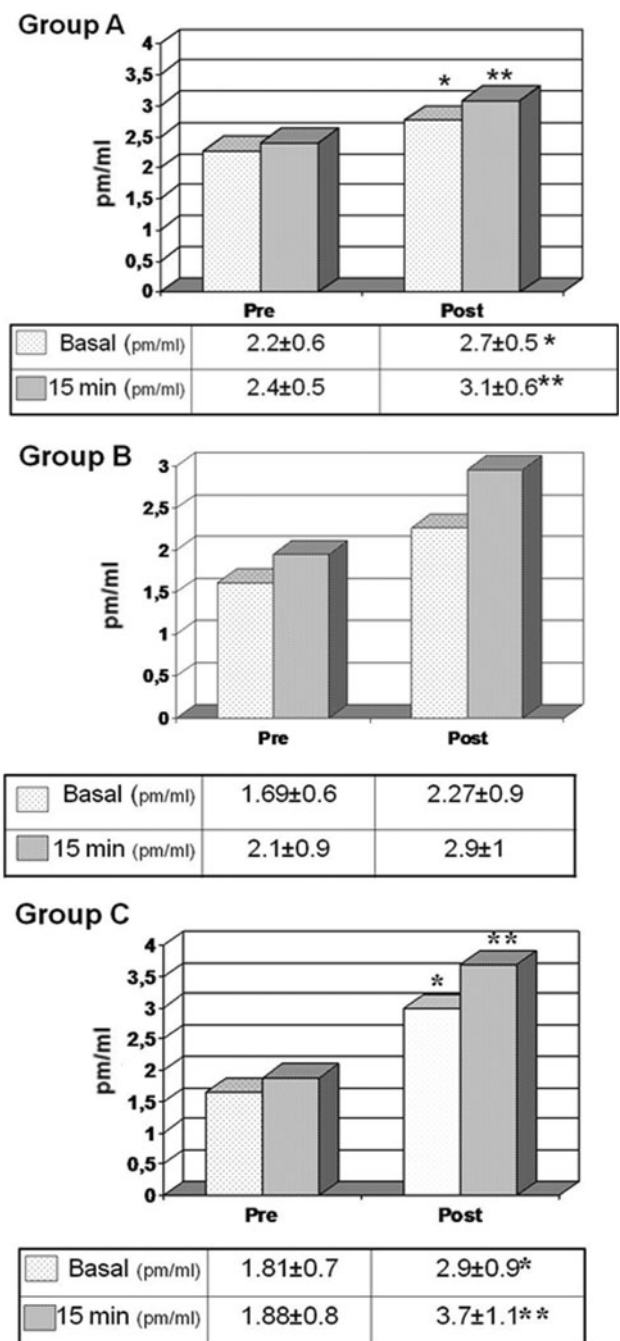


Fig. 6 GLP-1 values in basal conditions and at 15 min. During IVGTT before and after surgery in group A (<10 years of disease duration), group B (>10 years), and group C (nondiabetic obese patients); *,** $P < 0.005$ with preoperative values

Perioperatively, as shown in Figs. 8 and 9, in all groups we observed an early decrease of ghrelin values (statistically significant at the postoperative hour 6) and an increase of GLP-1 concentrations (statistically significant at postoperative hour 24 in group C). Total, AUC values for early and late insulin during IVGTT in each group are reported in Table 1.

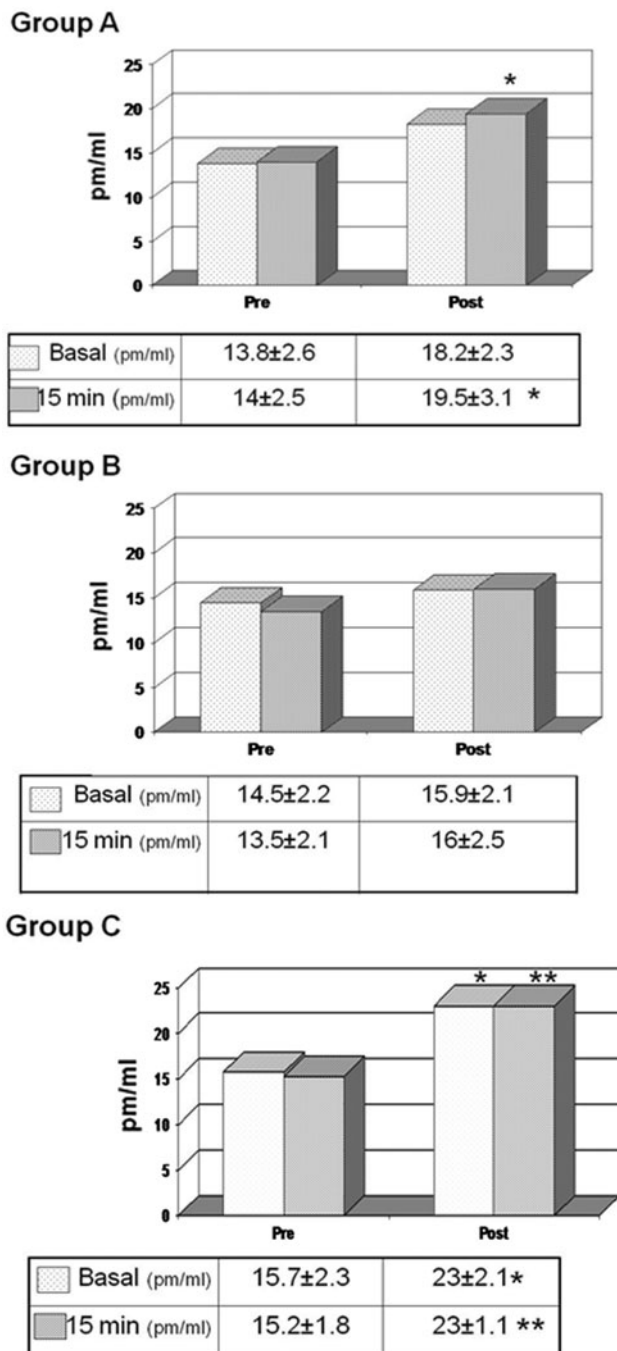


Fig. 7 PYY values in basal conditions and at 15 min. During IVGTT before and after surgery in group A (< 10 years of disease duration), group B (>10 years), and group C (nondiabetic obese patients); *,** $P < 0.005$ with preoperative values

Discussion

The prevalence of type 2 diabetes has markedly increased in the last decade with a matched increase in obesity. Ninety percent of type 2 diabetic patients are overweight or obese [11], confirming obesity as the primary risk factor for this disease. While medical treatment of obesity is

unsuccessful in maintaining long-term weight loss, bariatric surgery is able to achieve this goal and has a beneficial effect on comorbidities such as type 2 diabetes [12].

Weight loss is considered an important factor in improvement or resolution of type 2 diabetes [13]. Purely restrictive bariatric procedures such as gastric banding have been thought to improve diabetes by lowering caloric intake and by pure weight loss [14]. On the other hand, several bariatric procedures seem to trigger an antidiabetes mechanism beyond weight loss. At present, available evidence indicates that malabsorptive procedures may have several different weight-independent mechanisms for resolution of diabetes [15].

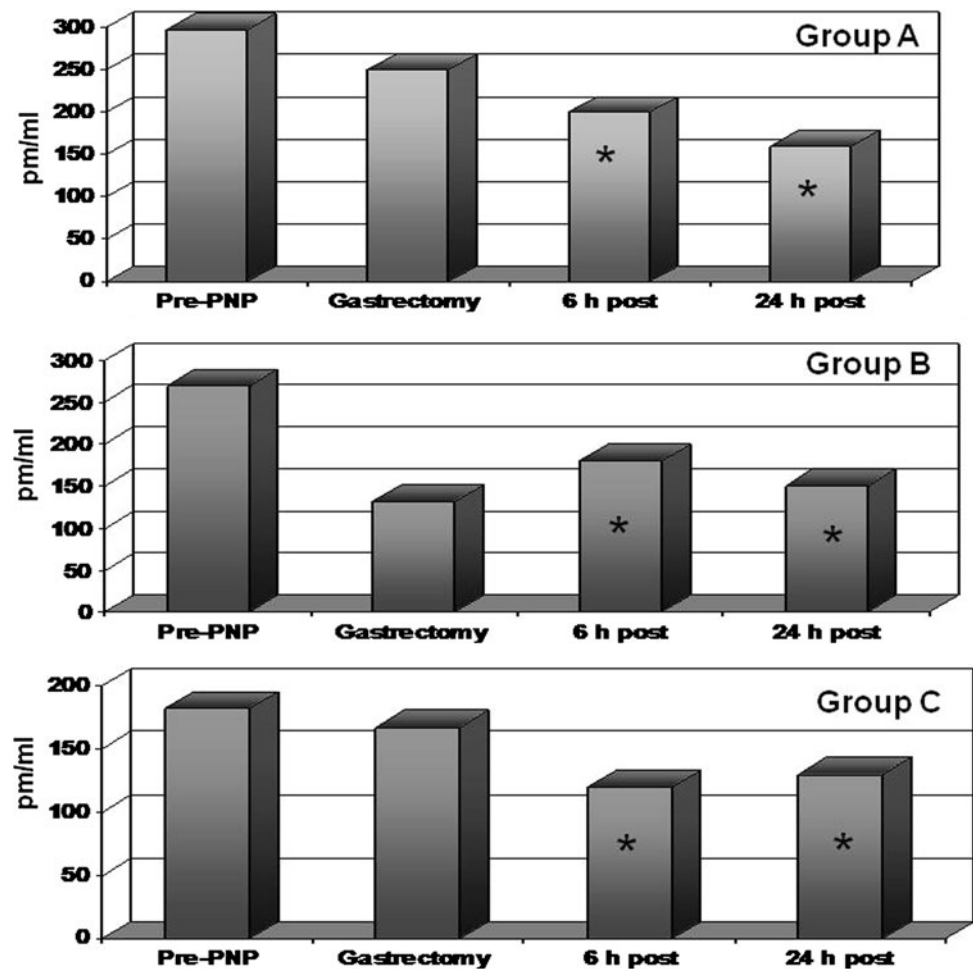
Evidence that weight loss and type 2 diabetes are not solely interdependent factors but that additional hormonal mechanisms may be involved has been provided by the data obtained from type 2 diabetes patients after GBP [16–18]. Rubino et al. [16] demonstrated that bypassing the duodenum and the upper jejunum in lean diabetic rats would return them to euglycemia, even though they maintained normal weight. Guidone et al. [19] found that BPD causes a prompt reversal of diabetes by normalizing peripheral insulin sensitivity soon after surgery and in the presence of a decrease of about 6 kg of body weight, mainly formed by fat mass.

Briatore et al. [20] demonstrated that BPD reduced insulin resistance in morbidly obese diabetic subjects and restored the acute insulin response a few weeks after surgery when all subjects had minimal body weight loss. Even more recently, Salinari et al. [9] found that in obese diabetic patients, the first phase of insulin secretion after the IVGTT and β -cell glucose sensitivity were fully normalized 1 month after BPD when a significant body weight loss was observed.

These findings suggest that changes in the gut hormonal milieu after BPD and GBP are relevant in the mechanism of type 2 diabetes remission, although in all subjects a minimal weight loss due to the bariatric surgery was present. Two pathophysiological hypotheses have been formulated: the “foregut” and the “hindgut” hypotheses. According to the former, the exclusion of the duodenum and proximal jejunum from the transit of nutrients may prevent the secretion of a putative signal that promotes insulin resistance and T2DM. In the latter, the control of diabetes results from the expedited delivery of nutrient chyme to the distal intestine, enhancing physiologic signals that improve glucose metabolism [21].

The main pathophysiological defects in the development of type 2 diabetes are β -cell dysfunction and insulin resistance. The β -cell function in type 2 diabetes is characterized by a progressive decline, from the disappearance of the first phase of glucose-induced insulin secretion to the impairment of the second-phase of insulin secretion. The

Fig. 8 Intra- and perioperative ghrelin modifications in groups A, B, and C; * $P < 0.05$ with prepneumoperitoneum values



early insulin response disappears, even in the early stages of the disease. This defect is important because the first-phase insulin secretion seems to have the greatest impact on postprandial plasma glucose excursions [22], which determines postprandial hyperglycemia. Our data show that diabetic obese patients who undergo SG obtain an amelioration in the pattern of insulin secretion and insulin sensitivity immediately after surgery, before any weight loss and before any food intake. In fact, both first phase and second phase improve before any weight loss and in absence of food passage into the small bowel. The former is shown by the restoration of a prompt peak of insulin plasma concentration after glucose infusion in patients who had a history of the disease for less than 10.5 years. The latter is shown by the reduction in the amount of insulin required to reduce the glucose concentrations during the last part of the test, suggesting that there is a beneficial effect of this procedure on diabetes by the improvement of insulin sensitivity. The latter findings occurred in all groups, even in patients with a long history of diabetes in whom restoration of the first phase of insulin secretion was not observed. The positive effect of SG on diabetes seems

to be related not only to the reduction of fat mass, as expected as a late effect, but also to the extensive resection of the gastric fundus that could be, per se, a factor that determines pathophysiological changes that are able to improve type 2 diabetes.

The ability to restore the β -cell function by SG could be partially confirmed by the lack of this positive effect in patients with a long history of the disease in whom insulin-secreting cells are severely compromised. In fact, the results obtained by us seem to indicate that the duration of the diabetic state is of paramount importance in whether SG fully exerts its effects on the glycemic metabolism, although the hormonal changes seen in this group of patients seem to follow the general trend seen in those with diabetes for <10.5 years. In this respect our findings are in accord with those of the literature and suggest that having diabetes for 10 years is a cutoff prognostic factor for the SG effect on diabetes [23].

Thus, the present investigation suggests the hypothesis that an extra pancreatic and/or extra intestinal (small bowel) factor, able to interfere with insulin secretion, can be put in action by the SG procedure.

Fig. 9 Intra- and perioperative GLP-1 modifications in groups A, B, and C; * $P < 0.05$ with prepneumoperitoneum values

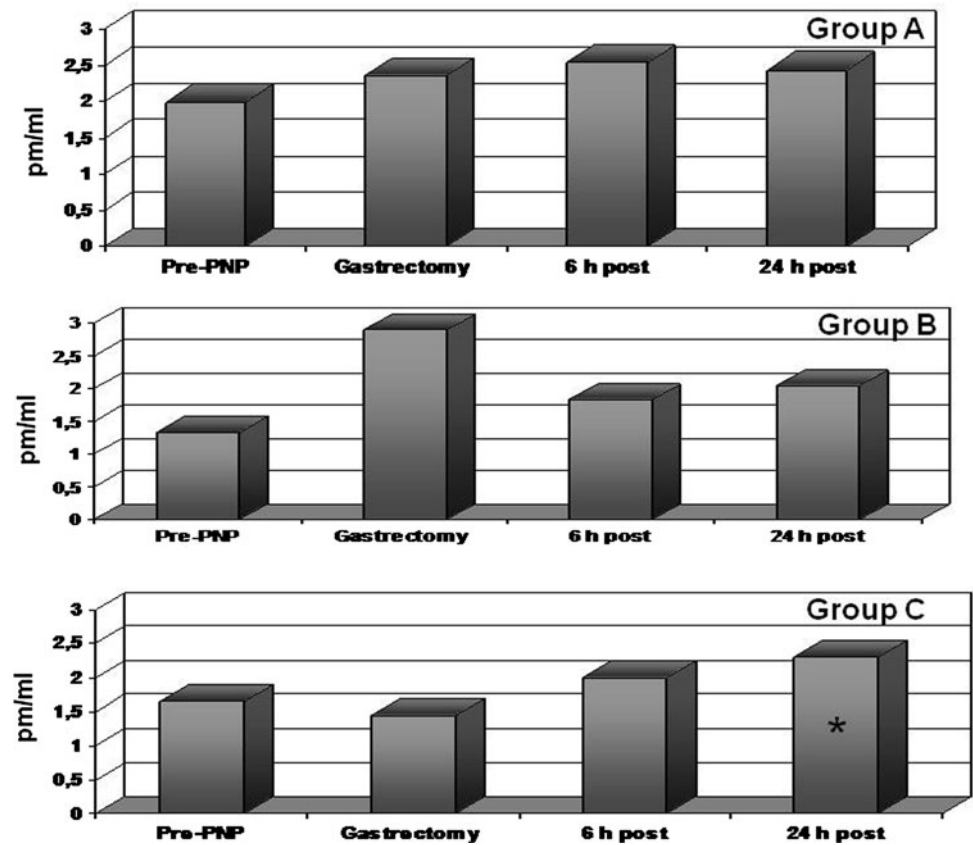


Table 1 Basal plasma insulin, glucose, and insulin AUC before and after surgery in different groups

	Before SG	After SG	<i>P</i>
Group A			
Basal insulin (μ UI/ml)	10.76 \pm 7.72	9.92 \pm 4.69	n.s.
Basal glucose (mg/dl)	97.2 \pm 27.1	101.4 \pm 14.0	n.s.
Total insulin AUC (μ UI ml ⁻¹ min)	7,053 \pm 1200	6,479 \pm 1065	n.s.
Early insulin AUC (μ UI ml ⁻¹ min)	133 \pm 27.7	254 \pm 22.4	0.012
Late insulin AUC (μ UI ml ⁻¹ min)	5,275 \pm 760	3,552 \pm 534	0.04
Group B			
Basal insulin (μ UI/ml)	6.61 \pm 2.44	6.63 \pm 4.08	n.s.
Basal glucose (mg/dl)	144 \pm 35.4	147.7 \pm 45.6	n.s.
Total insulin AUC (μ UI ml ⁻¹ min)	4,063 \pm 267	2,180 \pm 202	n.s.
Early insulin AUC (μ UI ml ⁻¹ min)	54.35 \pm 12.4	47.05 \pm 9.85	n.s.
Late AUC (μ UI ml ⁻¹ min)	3,891 \pm 401	1,825 \pm 231	0.04
Group C			
Basal insulin (μ UI/ml)	13.20 \pm 8.26	10.15 \pm 5.49	n.s.
Basal glucose (mg/dl)	92.6 \pm 8.7	88.6 \pm 15.2	n.s.
Total insulin AUC (μ UI ml ⁻¹ min)	27,545 \pm 2340	6,318 \pm 978	n.s.
Early insulin AUC (μ UI ml ⁻¹ min)	295 \pm 34.12	309 \pm 37.6	n.s.
Late insulin AUC (μ UI ml ⁻¹ min)	15,906 \pm 1297	3,156 \pm 432	0.028

AUC area under the curve, n.s. not significant

Recently, Kubosaki et al. [24] and Henquin et al. [25] clearly showed that the first-phase insulin secretion, which was absent in vivo in mice with a double knockout for islet

antigen 2 and 2 β , was fully restored in the islets of the same animals studied in vitro, suggesting the existence of factors, extrinsic to the islets, that can inhibit the “in vivo”

insulin response to an intraperitoneal glucose challenge. In analogy with this hypothesis, we suggest that the “factor” that inhibits insulin secretion can be produced in the stomach and that the excision of the gastric fundus, as occurs in SG, can interfere with its synthesis and/or delivery into the circulatory system, allowing the restoration of the first phase of insulin secretion.

Plasma ghrelin concentrations are demonstrated to be closely related to the amount of ghrelin-secreting cell removed by surgery [26, 27]. Indeed, ghrelin has been demonstrated to be suppressed by insulin and to inhibit glucose-induced insulin release by a mechanism not involving growth hormone (GH) or insulin resistance. Furthermore, both the first and second phases of glucose-induced insulin release were significantly enhanced by blocking the growth hormone secretagogue receptor (GHS-R) of ghrelin [28]. The marked effect of SG on ghrelin levels, as has been reported [29] and that has been confirmed by the present study, may suggest that this hormone could be involved in this process: ghrelin infusion is reported to increase insulin resistance and then the removal of the gastric fundus might contribute to improving insulin sensitivity [30].

In experimental studies, Karamanakos et al. [29] showed a significant increase in both fasting and postprandial PYY levels and a marked reduction in fasting ghrelin levels after SG. PYY is cosecreted with GLP-1 from intestinal L cells in response to food intake. As with ghrelin, there are recent studies that suggest a direct effect of PYY on insulin sensitivity [31].

Both in vivo and in vitro studies showed that GLP-1 in pancreatic β cells stimulates insulin biosynthesis. In addition to its insulinotropic effects, GLP-1 exerts glucose-lowering effects through inhibition of gastric emptying, restoration of insulin sensitivity, and inhibition of glucagon secretion, which may result in the decrease of hepatic glucose production [32, 33].

The results of the present study confirm the Peterli et al. [10] results on the effect of SG on GLP-1, PYY, and ghrelin levels. As did Peterli et al., we obtained in all patients a reduction in early-fasting and glucose-stimulated ghrelin values and an increase in fasting and stimulated GLP-1 and PYY levels. However, in addition to the findings of Peterli et al., the data of our study suggest that these changes are unrelated to weight loss or to hormonal effects induced by nutrient stimulation of the small bowel. The changes in the ghrelin, GLP-1, and PYY levels subsequent to SG seem to be triggered by SG per se. Moreover, the perioperative data seem to suggest that the SG effect on the modification of ghrelin and GLP-1 values occurs very early during the first postoperative day. Modifications of ghrelin, GLP-1, and PYY induced by SG all have an insulinotropic effect and may determine the early (72 h) modifications on

first-phase insulin secretion and on insulin sensitivity observed in these same circumstances.

Although the fundectomy explains the modification in ghrelin levels, the pathophysiological mechanism by which SG per se induces changes in no-meal-related GLP-1 and PYY values is unclear. When nutrients are ingested the release of GLP-1 (cosecreted with PYY) into the circulation occurs in a biphasic manner, consisting of a rapid (10–15 min) early phase followed by a more prolonged (30–60 min) second phase [34]. A direct stimulation of the L cells by digested nutrients is responsible for the second phase of peptides release subsequent to the rapid food passage through the distal small bowel (hindgut hypothesis). The vagus nerve, the neurotransmitter gastrin-releasing peptide (GRP), and the hormone glucose-dependent insulinotropic peptide seem to contribute to this rapid release of GLP-1 from L cells in the first phase [35]. Under the conditions of the present study, SG patients were not allowed any nutrients postoperatively prior to the IVGTT test so that direct stimulation of the L cells may be conceivably ruled out. It may be speculated that the diminished HCl production induced by the significant reduction of oxyntic cell mass stimulates the vagally innervated antral mucosa, left intact by SG, to secrete GRP and as a consequence gastrin and GLP-1 (Fig. 10).

Finally, it is important to stress that the protocol of this study was planned to include an identical period of 72 h of starvation preceding IVGTT before and after surgery so that each patient served as his own control. Thus, misleading factors in the interpretation of the results due to the well-known effect of starvation per se should be minimized and the pre- and postoperative differences found in diabetics can be confidently attributed to a sleeve gastrectomy per se effect.

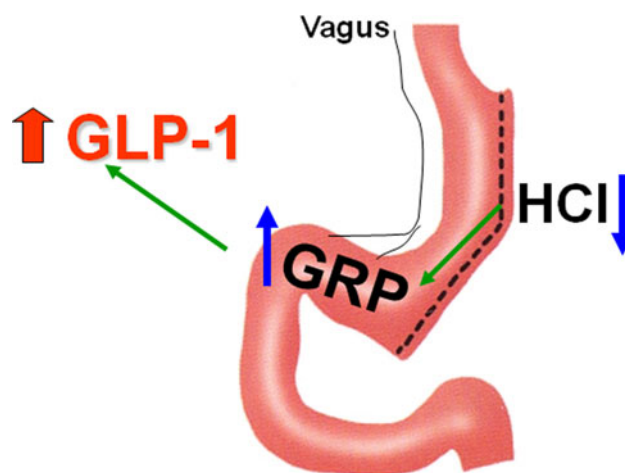


Fig. 10 The gastric hypothesis. Decreased HCl production induced by sleeve gastrectomy may act on the innervated antrum to produce gastrin-releasing peptide responsible for GLP-1 early-phase secretion [35]

Another criticism of our study that can be raised is the lack of a control group to rule out the early postoperative effects from general anesthesia and the stress of surgery. Although this is a weakness of the study that might limit our conclusions, it is well known that postoperative stress should worsen the glycemic control and the conditions of insulin resistance, contrary to what we have found.

Finally, it is important to follow these patients for a longer postoperative period to confirm these data; however, in accord with the present study's results, Peterli et al. [10] demonstrated a marked increase in both plasma insulin and GLP-1 levels favoring improved glucose homeostasis 1 week and 3 months postoperatively.

Conclusions

In summary, prompt restoration of insulin secretion and improvement in insulin sensitivity in type 2 diabetic obese patients with a history of diabetes of <10 years seem to be related to changes in some gastric factor(s) as a direct consequence of SG, independent from weight loss and food passage through the small bowel. Ghrelin, GLP-1, and PYY changes induced by SG may play a role in these pathophysiological changes, highlighting a role of the stomach in the regulation of the glucose metabolism. A history of the disease of about 10 years seems to suggest a hypothetical cutoff in the regulation of glucose homeostasis induced by SG. A gastric hypothesis, along with the foregut and the hindgut hypotheses, may be put forward to elucidate the effects of bariatric surgery, as far as SG is concerned, on T2DM.

These observations may have clinical relevance in evaluating the role and the indications of surgery in general, and of SG in particular, in proposed surgical therapy for T2DM in obese patients. A number of questions still need to be answered and a number of hypotheses still need confirmation to fully comprehend the role of SG in the treatment of T2DM; however, the results so far obtained are encouraging and should stimulate further studies.

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