ORIGINAL CONTRIBUTIONS

Weight Regain After Gastric Bypass: Influence of Gut Hormones

Marco Aurelio Santo [1] · Daniel Riccioppo [1] · Denis Pajecki [1] · Flavio Kawamoto [1] ·
Roberto de Cleva [1] · Leila Antonangelo [1,2] · Lia Marçal [1,2] · Ivan Cecconello [1]

Abstract

Background The Roux-en-Y gastric bypass (RYGB) is the gold standard bariatric operation. However, a major concern in late follow-up is the substantial weight regain. Understanding the role of gastrointestinal hormone secretion in this situation is relevant.

Methods The aim of the present study was to evaluate the influence of gastrointestinal hormones comparing postprandial secretion of ghrelin, glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide 1 (GLP-1), and leptin between patients with weight regain and those with favorable weight control. Twenty-four patients with follow-up from 27 to 59 months were divided into two groups according to sustained weight loss: group A (14 patients) had sustained weight losses, and group B (10 patients) had significant weight regain. Basal serum levels of ghrelin, GIP, GLP-1, and leptin after fasting and 30, 60, 90, and 120 min after a standard meal were measured.

Results There was no difference in the ghrelin secretion. There was a difference in the GIP secretion, with a higher percentage increase in 30 min in group A (330 %×192.2 %; $p=0.01$). There were also differences in the GLP-1 secretion, with higher increases in absolute ($p=0.03$) and percentage values after 30 min in group A (124 %×46.5 %; $p=0.01$). There was also a difference between baseline leptin values, with higher levels in group B ($p=0.02$).

Conclusions The secretion of gut hormones in patients with weight regain after RYGB is different from that in patients with satisfactory weight outcome. After meal stimulation, reduced levels of GIP and GLP-1 may indicate the influence of gut hormones in the process of weight regain.

Keywords Morbid obesity · Bariatric surgery · Weight regain after bariatric surgery · Weight regain postgastric bypass · GLP-1 · Incretins

✉ Marco Aurelio Santo
santomarco@uol.com.br

Daniel Riccioppo
danriccioppo@me.com

Denis Pajecki
pajecki@netpoint.com.br

Flavio Kawamoto
flaviomk@yahoo.com

Roberto de Cleva
roberto.cleva@uol.com.br

Leila Antonangelo
l.antonangelo@hc.fm.usp.br

Lia Marçal
liamarcal@hotmail.com

Ivan Cecconello
icecconello@hotmail.com

[1] Department of Digestive Surgery, University of São Paulo School of Medicine, Av. Arnolfo Azevedo 208, São Paulo, SP 05673-010, Brazil

[2] Central Laboratory of Hospital das Clínicas, São Paulo, Brazil

Introduction

A major concern in the late follow-up of obese patients subjected to surgical treatment is the recurrence of obesity, sometimes reaching values similar to those measured in the preoperative period, characterizing failure of the procedure [1–4].

After the nadir of weight loss, which occurs around 18 months after Roux-en-Y gastric bypass (RYGB) with approximately 65 % of excess weight loss (%EWL) [5–7], studies have reported that the rate of failure based on weight regain ranges from 5 to 30 %, increasing the longer the follow-

up, particularly among super obese patients [6, 8–12]. Experimental studies indicate weight regain in approximately 25 % [13].

The feeling of satiety after food intake contributes to the maintenance of weight loss, a phenomenon that is observed early after surgery and is mediated by gastrointestinal hormones [14], which influence hunger and energy balance by regulating the intake, storage, and energy expenditure [15]. The response of the gastrointestinal tract to nutrient ingestion is caused by the secretion of several gastrointestinal hormones, in particular glucagon-like peptide 1 (GLP-1) [16]. Other enterohormones, including ghrelin, glucose-dependent insulinotropic polypeptide (GIP), and the adipokine leptin, play a role in the entero-hypothalamic axis.

The aim of this study is to evaluate the influence of the secretion of gastrointestinal hormones and adipokines in the late postoperative period among patients subjected to RYGB by comparing the postprandial secretion of ghrelin, GIP, GLP-1, and leptin between patients who regained weight and those with satisfactory weight control.

Materials and Methods

A total of 24 patients submitted to RYGB (gastric pouch <50 mL with an alimentary and a biliopancreatic loop of 100 and 60 cm, respectively) between 2006 and 2011 for the treatment of morbid obesity were evaluated. All patients had BMIs >40 kg/m^2. The patients were selected considering a minimum follow-up period of 26 months, from the time of surgery until the last weight assessment conducted between July 2013 and January 2014.

The patients were divided into groups according to weight loss sustenance that was calculated by the relationship between the %EWL (ideal weight based on the BMI of 25 kg/m^2) at the last weight assessment and the maximum %EWL reached [1−(last%EWL/maximum%EWL)], which in fact represents the amount of weight regain of the maximum weight lost, expressed as percentages:

- Group A: successful weight loss sustenance after the initial successful weight loss (maximum %EWL >50 %) and maintaining up to 50 % of the weight lost

– Subgroup A1: excellent, with regain of <10 % of the weight lost
– Subgroup A2: regular, with regain corresponding to 10–50 % of the weight lost

- Group B: unsatisfactory weight loss sustenance after the initial successful weight loss, with regain of >50 % of the weight lost

The presence of a gastro-gastric fistula was excluded after endoscopy and contrast radiography.

The enterohormone secretion was measured by the serum levels of ghrelin, GIP, GLP-1, and leptin at fasting ($t0$) and after ingestion of a standard meal at 30 min ($t30$), 60 min ($t60$), 90 min ($t90$), and 120 min ($t120$). The values were compared between groups A and B and between subgroups A1 and A2. A standard meal consisted of one 200-mL bottle of Nutren™ 1.5 (Nestle Health Science) with approximately 300 kcal, with energy intake derived from proteins (14 %), carbohydrates (58 %), and fats (28 %). The blood samples were collected and centrifuged at 4 °C, with the plasma separated and frozen at −70 °C. The biomarker test was performed by Bio-Plex Pro™ Diabetes Assays. The Bio-Plex Manager software (Bio-Rad Laboratories, Hercules, CA, USA) was used to make the dosage curve, and the levels are expressed in picograms per milliliter.

The study was approved by the Research Ethics Committee of the Department of Digestive Surgery, University of São Paulo School of Medicine, protocol No. 324454, July 3, 2013.

Statistical Analysis: The quantitative variables were expressed as the means±standard error, and the qualitative variables were expressed as percentages. To compare the groups during the evaluation periods, the Anderson–Darling test, Student's t test, and Mann–Whitney test were used. Interactions between the groups were evaluated using non-parametric repeated measures analysis of variance (ANOVA) [17, 18]. Evidence was considered significant for p values smaller than 5 % ($p<0.05$).

Results

The classification into groups A (14 patients) and B (10 patients) is shown in Fig. 1. The mean ages were similar between the groups at the time of surgery, corresponding to 41.5±3.07 and 40.8±3.72 years, respectively ($p=0.88$).

Preoperative: Weight and BMI were 128.2±5.43 kg and 49.8±2.31 kg/m^2 for group A and 144.3±12.24 kg and 53.6±3.17 kg/m^2 for group B with no differences ($p=0.37$ and 0.19).

Maximum %EWL in the Postoperative: The average period to reach maximum %EWL postoperatively was 18 months (20.4 months in group A and 14.7 in group B). The average minimum weight and BMI were 73.4±3.69 kg and 28.5±1.46 kg/m^2 in group A and 91.1±6.4 kg and 34.0±2.02 kg/m^2 in group B. The average maximum %EWLs reached were 81.8 %±3.51 in group A and 64.7 %±5.9 in group B. Despite the significant difference between these two groups ($p=0.02$), indicating that weight loss was greater in group A, the patients in both of the groups achieved success in terms of loss of excess weight (>50 %), except for one patient from group B (%EWL of 32.9 %).
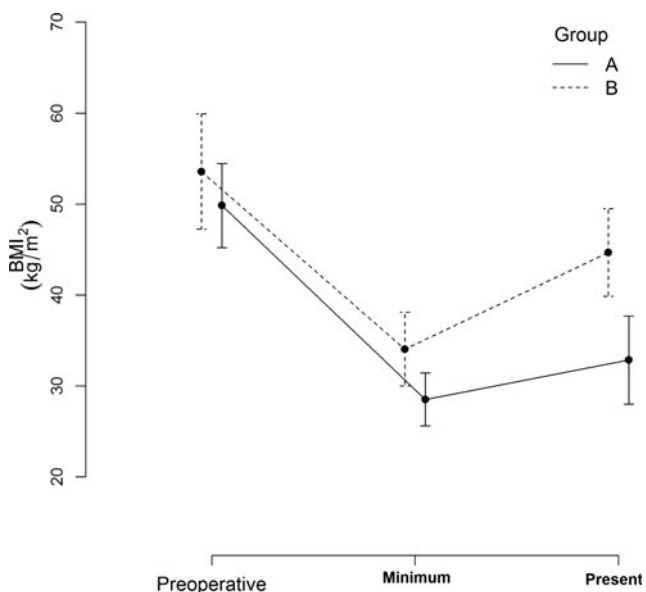
Fig. 1 BMIs in the preoperative period and when the minimum and present weights were reached

Present Weight: The average period elapsed from the time of the maximum %EWL until the present assessment was 40.7 months (27.2 in group A and 59.7 in group B). At the present assessment, the average BMI was 32.8 ± 2.41 kg/m^2 in group A and 44.7 ± 2.41 kg/m^2 in group B ($p=0.002$). In this instance, the average %EWLs were $67.2\% \pm 5.98$ in group A and $29.3\% \pm 2.98$ in group B ($p<0.001$). The amounts of weight regain of the weight lost, expressed in percentages, were $19.6\% \pm 4.68$ in group A (seven patients in each subgroup) and $55\% \pm 1.58$ in group B ($p<0.001$).

Ghrelin: No difference was observed between the absolute baseline ghrelin levels between groups A and B ($p=0.5$). After meal, also no difference in absolute values ($p=0.4$) and in the percentage changes between the groups were observed at any time interval ($p=0.9$, $p=0.6$, $p=0.3$, and $p=0.2$, respectively; Fig. 2). For the subgroups A1 and A2, the average percentage changes at $t30$ were -0.7 and 0.8%, respectively, with no difference between the subgroups during the periods evaluated.

GIP: there was no difference between the absolute baseline GIP levels between the two groups ($p=0.3$). After meal, an increase in the GIP level was observed at $t30$, followed by decreased levels at $t60$, $t90$, and $t120$ in both of the groups. The absolute values over time were similar in both of the groups ($p=0.2$), but the percentage increase relative to baseline levels at $t30$ was significantly higher in group A (330.0 %) compared with the increase in group B (192.2 %; $p=0.01$). No differences in percentage changes were observed at follow time interval ($p=0.1$, $p=0.07$, and $p=0.1$, respectively; Fig. 3). For the subgroups A1 and A2, the average percentage increases at $t30$ were 320.8 and 339.2 %, respectively, with no difference between the subgroups during the periods evaluated.
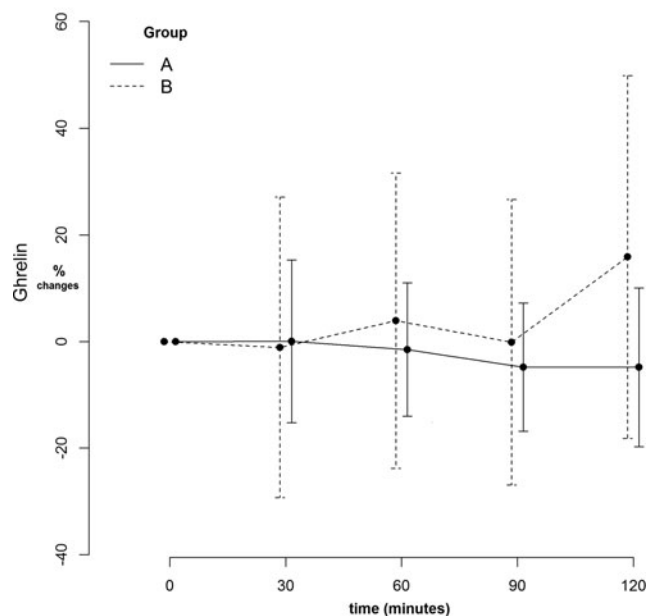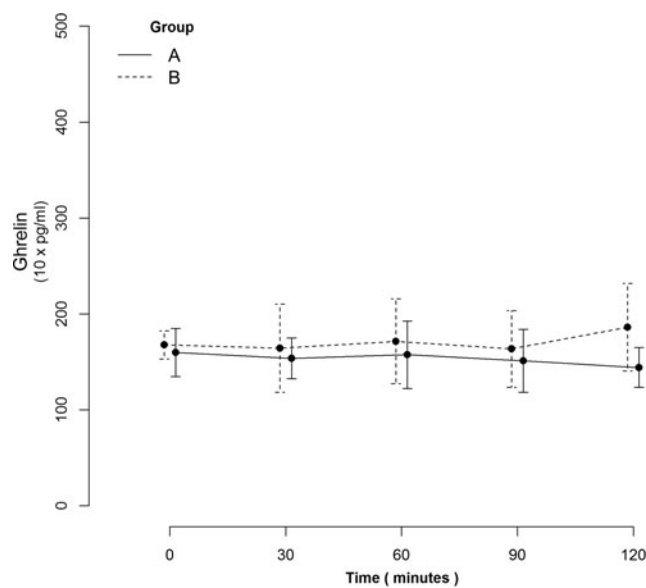
Fig. 2 Ghrelin secretion levels and percentage changes relative to baseline levels after ingestion of a standard meal

GLP-1: There was no difference between the absolute baseline GLP-1 levels between groups A and B ($p=0.1$). After meal, increases in the GLP-1 level were observed at $t30$, followed by decreased levels at $t60$, $t90$, and $t120$ in both of the groups, but the increase in group A was significantly higher than that in group B ($p=0.03$). At $t30$, the percentage increase relative to baseline levels was significantly higher in group A (124.0 %) compared with that in group B (46.5 %; $p=0.01$). The percentage changes did not differ significantly at follow time interval ($p=0.2$, $p=0.2$, and $p=0.8$, respectively; Fig. 4). For the subgroups A1 and A2, the average percentage increases at $t30$ were 120.4 and 127.5 %, respectively, with no difference between the subgroups during the periods evaluated.
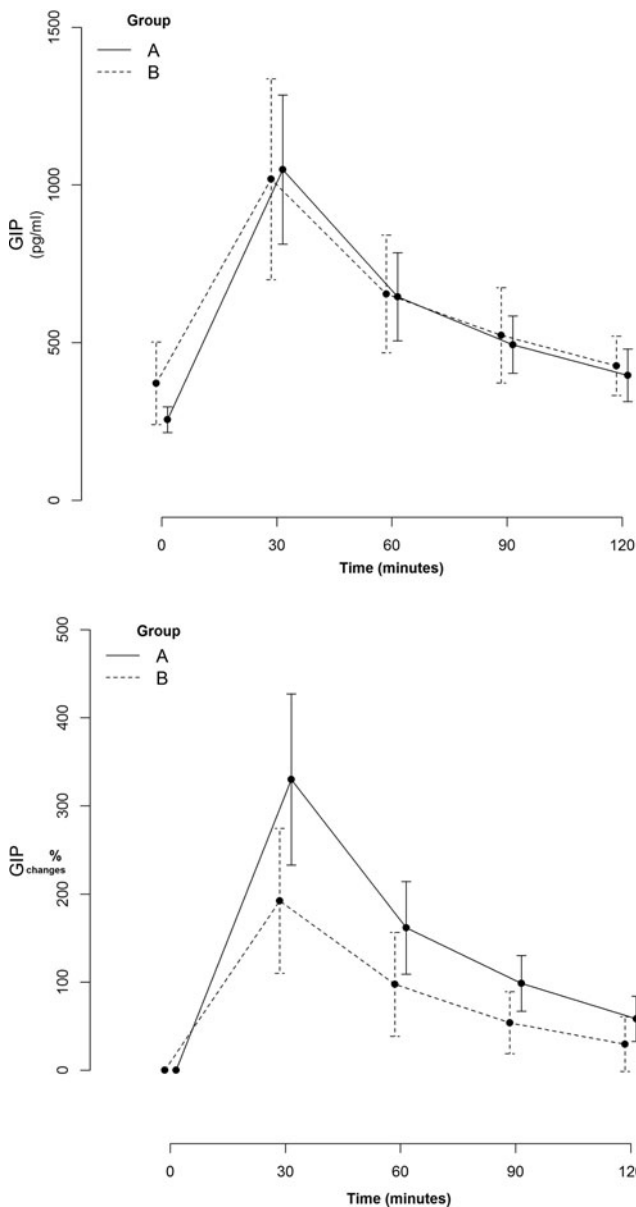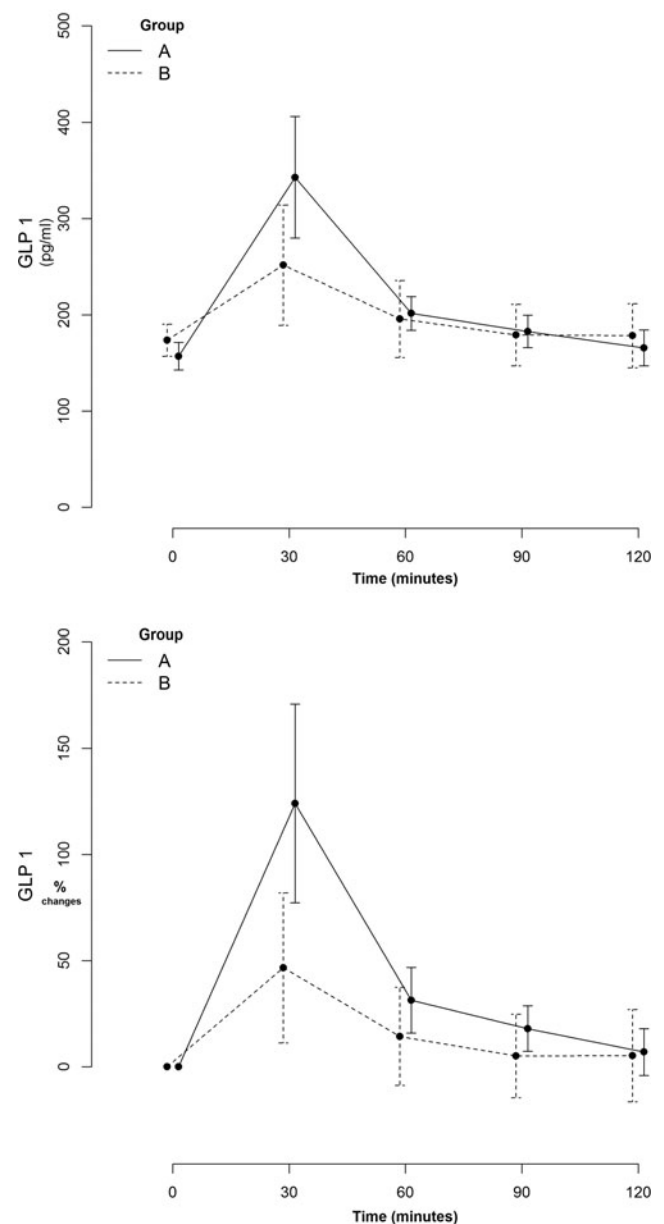
Fig. 3 GIP secretion levels and percentage changes relative to baseline levels after ingestion of a standard meal

Fig. 4 GLP-1 secretion levels and percentage changes relative to baseline levels after ingestion of a standard meal

Leptin: There was a difference in the absolute baseline leptin levels between groups A and B ($p=0.02$). After meal, minor changes in the leptin levels were observed at follow time interval in both of the groups (Fig. 5). For the subgroups A1 and A2, the absolute baseline levels were 5908.3 and 10, 024.3 pg/mL, respectively, followed by minor changes.

Discussion

The weight course after RYGB presents a similar clinical trend in many patients, as reported by Christou et al. [19], with a progressive decrease until the minimum weight is reached between 18 and 24 months after surgery, followed by a propensity to regain weight. As weight regain occurs, the lack of well-defined criteria to characterize the failure becomes evident [20]. We used the amount of weight regain of the maximum weight lost, expressed as percentages. Therefore, when weight regain was >50 % of the weight lost, the outcome was considered failed.

Considering that changes in the anatomy of the digestive tract after RYGB are accompanied by changes in hormonal secretion, affecting weight control and glucose homeostasis [21–32], the outcomes probably improve as these hormonal adjustments persist. These adjustments depend on the emptying of the gastric pouch, and reaching more promptly the small intestine promotes the rapid exposure of the intestinal epithelium to nutrients [33].
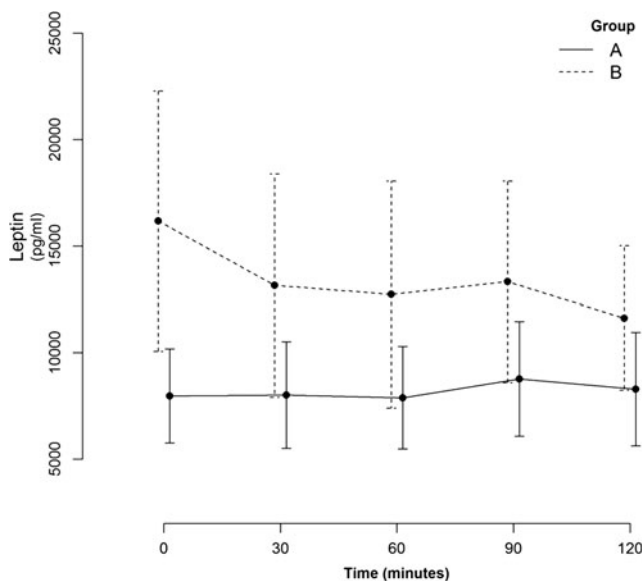
Fig. 5 Leptin secretion levels at baseline and after ingestion of a standard meal

During weight regain, an imbalance of this process may occur, but this mechanism needs to be elucidated.

Decreased ghrelin levels were reported after RYGB; certainly, this change in hormonal secretion affects weight loss by regulating appetite control [16, 34, 35]. The fact that the baseline levels of ghrelin were similar in groups A and B indicates that these levels did not significantly increase in the group who regained weight. A review study reported a correlation between ghrelin levels and energy balance and observed that ghrelin levels in obese subjects and among those with larger fat mass are generally decreased [36]. However, the long-term secretion of ghrelin and its effect on weight regain have not been fully elucidated.

Previous studies differ with regard to the change in GIP levels after bariatric surgery. Some studies have shown decreased GIP levels at fasting in patients with diabetes [37] and in the postprandial period [38], whereas other studies have shown increased secretion in the postprandial period, with consequent favorable metabolic effects [39, 40], although there is a discussion whether the changes in GIP levels persist 1 year after RYGB [39]. The most important role of GIP is likely associated with glucose metabolism via the incretin effect because some degree of resistance to the effects of GIP has been reported in patients with diabetes [41].

The analysis of the percentage change after nutrient intake indicates that the increase in GIP levels was more pronounced in group A, suggesting that the GIP secretion profile among individuals with satisfactory weight control was distinct from that of individuals with weight regain, likely indicating a tendency to restore the secretory process, a phenomenon observed after glucose control in patients with diabetes [42]. This difference is also evident in individualized evaluations, in which approximately 80 %

subjects from group A showed large percentage changes, unlike group B, in which only 20 % presented increases exceeding 200 % relative to baseline levels. The postprandial increases in GIP levels in subgroups A1 and A2 were similar, indicating that patients with intermediate weight regain retained a secretory profile similar to that of patients with excellent weight control.

Several studies have demonstrated the effect of bariatric surgery on GLP-1 secretion. The preprandial baseline GLP-1 levels were similar in both groups studied. Although decreased GLP-1 levels at fasting after RYGB have been reported [43], which may suggest that an increased baseline level could be expected in the group with a satisfactory course, we highlight that GLP-1 is likely stimulated in response to a meal [44].

The increase in the absolute values relative to baseline in the postprandial period in group A appears to be significantly greater than that in group B. Furthermore, the analysis of the percentage change soon after nutrient intake indicates that the increase in group A was significantly higher than that in group B, suggesting that the GLP-1 secretion profile is distinct among individuals with satisfactory weight control compared to individuals with weight regain. This difference is also evident in the individualized evaluation, where approximately 65 % patients from group A showed large percentage changes in the postprandial period, unlike group B, in which only 10 % presented increases exceeding 100 % relative to the baseline levels.

Other studies [14, 39, 45, 46] showed that patients subjected to RYGB with favorable outcome for weight loss presented higher GLP-1 levels compared with patients with less favorable weight loss, and the increase in GLP-1 levels after RYGB persisted 1 year after surgery. However, the patients who experienced weight regain after reaching a minimum weight in the postoperative period were not evaluated.

The similar GLP-1 secretion profiles between subgroups A1 and A2 with excellent and regular weight lost outcome, respectively, and the difference between groups A (satisfactory) and B (unsatisfactory) may suggest that some changes may occur at some point in the weight courses, followed by an attenuation of GLP-1 secretion, similar to what was observed during decreased insulin secretion in the natural course of type 2 diabetes; this mechanism could significantly influence weight regain.

The significant differences in the baseline leptin levels between the groups suggest that the energy reserves in group B were larger than those in group A owing to the higher accumulation of fat already established by weight regain. In this context, a direct correlation was noted between decreased BMI and decreased leptin levels after RYGB [47]. Therefore, the resistance to the satiety-inducing effects of leptin found in obese individuals may already be present in the operated patients who gradually regain weight.

Conclusion

Despite of low number of patients in each group, we can conclude that the secretion profile of gastrointestinal hormones among the patients who experienced weigh regain after RYGB differs from that for patients with satisfactory weight control. After nutrient intake, the decreased levels of GIP and GLP-1 may indicate the influence of these hormones in the process of weight regain.

Compliance with ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

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