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Endoscopic transoral outlet reduction induces enterohormonal changes in patients with weight regain after Roux-en-Y Gastric Bypass.

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Abstract:
Background and aims: Transoral outlet reduction (TORe) has long been employed in treating weight regain after Roux-en-Y gastric bypass. However, its impact on gut hormones and their relationship with weight loss remains unknown. Patients and Methods: This is a substudy of a previous randomized clinical trial. Adults with significant weight regain and dilated gastrojejunostomy underwent TORe with Argon Plasma Coagulation (APC) alone or APC plus endoscopic suturing (APC-Suture). Serum levels of ghrelin, GLP-1, and PYY were assessed at fasting, 30, 60, 90, and 120 minutes after a standardized liquid meal. Results were compared according to allocation group, clinical success, and history of cholecystectomy. Results: Thirty-six patients (19 APC vs. 17 APC-Suture) were enrolled. There were no significant baseline differences between groups. In all analyses, the typical postprandial decrease in ghrelin levels was delayed by 30 minutes, but no other changes were noted. GLP-1 levels significantly decreased at 12 months in both allocation groups. Similar findings were noted after dividing groups according to the history of cholecystectomy and clinical success. The APC cohort presented an increase in PYY levels at 90 minutes, while APC-Suture did not. Naïve patients had significantly lower PYY levels at baseline (p=0.01) compared to cholecystectomized individuals. This latter group experienced a significant increase in the AUC for PYY levels, while naïve patients did not, leading to a higher AUC at 12 months (p=0.0001). Conclusions: TORe interferes with the dynamics of gut hormones. APC triggers a more pronounced enteroendocrine response than APC-Suture, especially in cholecystectomized patients.

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Introduction

The Roux-en-Y Gastric Bypass (RYGB) is currently the second most common bariatric procedure in the world. [1] As of 2019, 45,000 RYGB procedures were performed in the United States. [2] It is safe and highly effective at promoting weight loss and controlling metabolic diseases. However, data show that almost half of patients regain more than 20% of the lost weight in the long term with dismal consequences. [3,4]

Since revisional surgical procedures for weight regain are risky, endoscopic alternatives have been proposed. When associated with dilated gastrojejunal anastomosis, level 1 data support the effectiveness of the transoral outlet reduction (TORe) with endoscopic suturing or argon plasma coagulation (APC) alone. [5] Several studies report favorable weight loss and comorbidities resolution, but few investigate the underlying physiology. [6,7] Some preliminary data suggest an increase in pouch retention may lead to enhanced satiety and better weight loss outcomes. [8] However, other studies directly contradict this finding and demonstrate a negative correlation between increased pouch retention and clinical success after TORE. [9]

Gut hormones play a major role in primary weight loss after bariatric surgery and in the context of significant weight regain. [10] The most implicated ones are ghrelin, Peptide YY (PYY), and the Glucagon-like peptide 1 (GLP-1). Cells from the gastric fundus produce and release ghrelin, which stimulates appetite and increases gastrointestinal motility. Cells in the distal ileum and colon produce and release PYY, which promotes satiation while reducing gastrointestinal motility. Finally, ileal enteroendocrine cells produce GLP-1, a peptide similar to PYY, except for an additional incretin effect. [11]

The impact of TORe on gut hormones and their relationship with weight loss and clinical success rates are still unknown. Moreover, understanding the hormonal dynamics after TORe could help create more thorough bariatric approaches. Therefore, we developed the present study to help elucidate part of the physiological pathway through which weight loss occurs after revision of the gastrojejunostomy.

Material and methods

Design and Registry

This is a branch of a previous single-center, pilot randomized trial with clinical results published elsewhere. [12] It was registered on the clinicaltrials.gov online database (NCT03094936) and had the Internal Review Board approval (Protocol number 1.857.932/2016).

Population

Adult patients (18-60 years old) with significant weight regain after RYGB (>20% from nadir weight) and dilated GJA (≥15mm) were randomly assigned to TORe with APC alone or APC plus endoscopic suturing with the Apollo Overstitch device (Apollo Endosurgery, Austin, TX, USA). Randomization was carried out using an online software (randomizer.org) with a 1:1 ratio in blocks of four. Allocation was performed using sealed opaque envelopes that were opened immediately before the procedures. Due to the need for repeat APC sessions (per protocol), blinding was not feasible. Patients with pregnancy, coagulopathy, moderate and severe erosive esophagitis, and concurrent use of anorexigenic drugs were excluded from the trial. All information on settings, endoscopic procedures, and follow-up strategy are described in the original trial.

As a pilot study, the sample size was 40 subjects (20 in each allocation group). All subjects underwent a standardized blood withdrawal protocol before the procedure and at one year of follow-up. Individuals attending both blood draw visits were considered eligible for the present study. In addition, the research team obtained formal written informed consent from all patients before enrollment in the trial.

Outcomes and definitions

The primary outcome was the whole-group change in serum levels of ghrelin, GLP-1, and PYY between baseline and 12 months. We planned secondary analyses comparing results according to allocation group and clinical success. Clinical success was defined as %TWL≥10% at 12 months, per previous protocol. [12] These comparisons included serum levels (in pg/mL), variation over time (behavior), and the area under the curve (AUC). Since ghrelin is an orexigenic hormone that induces hunger, its most crucial role in meal cessation occurs during the first minutes of the meal. Therefore, we analyzed and compared AUCs for ghrelin between times

0 and 30 minutes. As PYY and GLP-1 usually act on a later phase of the meal to regulate satiety and meal cessation, we analyzed and compared the AUC between 30 and 120 minutes.

Post-hoc analysis

After the trial's design, some articles described an exciting interaction between the gallbladder and the gut hormones responsible for mediating satiety, satiation, and gastrointestinal motility. [13,14] Therefore, we planned a post-hoc analysis to compare the levels and dynamics of ghrelin, GLP-1, and PYY in cholecystectomized versus non-cholecystectomized patients.

Blood draw protocol

Patients were instructed on 12-hour fasting prior to the gut hormones assessment. Serum levels of ghrelin, GLP-1, and PYY were measured at fasting, 30, 60, 90, and 120 minutes after ingestion of a standardized liquid meal. The meal consisted of a 200-mL bottle of Nutren 1.5 (Nestle Health Science) with 300 kcal and energy intake derived from carbohydrates (58%), fats (28%), and proteins (14%). This standardized institutional protocol has already been successfully employed in previous research projects. [10] The blood samples were collected in EDTA tubes and centrifuged under 4500rpm at 4°C, divided into 1.5mL aliquots, and then frozen at −20°C until all blood samples (baseline and follow-up) were available for the assessment of gut hormones. [15] The descriptive protocol for gut hormones assessment is available in the supplementary material 1.

Statistical analysis

Continuous variables were described as means with standard deviations and categorical as frequencies or percentages. We assessed the normality of the data and employed statistical tests accordingly. We used the chi-squared or Fisher exact test for comparisons between categorical variables and the Student T-test to compare continuous variables. The analysis of variance for repeated measures (ANOVA test) was used to analyze and compare the variation of hormonal levels over time. If we found no significant difference in the behavior between groups, their results were pooled and analyzed to compare values from different assessment times. If we detected a different behavior over time, they were analyzed separately. An experienced

statistician ran the analyses with SPSS v17.0 software (IBM Inc., Armonk, NY, USA). A p-value <.05 was considered statistically significant for a 95% confidence interval.

Results

Of the 40 patients enrolled in the main trial, 36 successfully underwent blood sampling at baseline and 12 months (36/40, 90% follow-up rate) and were included in the present study (Figure 1). Nineteen patients underwent APC alone, and 17 underwent APC plus endoscopic suturing. Baseline characteristics were similar between the allocation groups. Table 1 summarizes demographics, past medical history, and baseline tests.

FIGURE 1

TABLE 1

APC vs. APC+Suture.

Ghrelin levels

The allocation groups presented similar levels at the time points (p=0.075) and behavior over time (p=0.13). Both groups had statistically significant changes in ghrelin levels throughout the assessments (p=0.018). At baseline, both groups experienced a statistically significant decrease in ghrelin levels from 0 to 30min (p=0.001) and from 0 to 60min (p=0.005). At 12 months, the decrease was delayed and occurred between 0 and 60min (p=0.006) and between times 0 and 90min (p=0.013). Table 2 summarizes the ghrelin levels according to group and assessment times, and the comparisons between times of assessment for both groups. Figure 2 depicts the behavior of ghrelin levels over time.

The AUC between times 0 and 30min for ghrelin was different between groups at baseline and 12 months (695 ± 463 vs. 504 ±198, and 892 ± 1,104 vs. 481 ± 271, p=0.03 for APC and APC+suture at baseline and 12 months, respectively). However, there was neither

difference in behavior over time (p=0.43) nor statistically significant changes between baseline and 12 months within the same allocation group.

GLP-1 levels

The allocation groups presented similar levels at the time points (p=0.22) and behavior over time (p=0.26). Both groups had statistically significant changes in GLP-1 levels throughout the assessments (p=0.001). Baseline values were significantly higher throughout the entire evaluation than the follow-up levels (p<0.001). At baseline and 12 months, both groups experienced a statistically significant increase in GLP-1 levels from times 0 to the other assessments (Table 2, Figure 2).

Concerning the AUC between times 30 and 120min, the means were similar (p=0.15) between APC and APC + Suture groups at baseline (3379 ± 1,940 vs. 2,571 ± 1,393) and 12 months (2,165 ± 2108 vs. 1,369 ± 794). Both groups presented a statistically significant decrease in the AUC between 30 and 120min from baseline to 12 months (p<0.001). Nonetheless, the decrease was similar between groups (p=0.64).

PYY levels

The allocation groups presented different behavior over time in PYY levels (p=0.006) and different fasting baseline values (p=0.006). The APC group had similar means comparing baseline and 12 months levels, except for a statistically significant increase at 90min (131±76.1 *vs.* 185.5±87, p=0.017). Patients in the APC+suture group experienced no difference in preprocedural versus follow-up PYY levels at all time points. Still, both groups had a statistically significant increase in PYY from time 0 to all other assessments at baseline and 12 months (Table 2, Figure 2).

The groups had different trends concerning the AUC between 30 and 120min (p=0.03). While the APC group experienced an increase from baseline to follow-up (15,937 ± 7,346 vs. 19,521 ± 7,941, p=0.02), the APC + Suture group presented a non-significant decrease (14,486 ± 7,597 vs. 13,146 ± 5,767, p=0.41).

FIGURE 2

TABLE 2

Clinical Success (CS) vs. Clinical Failure (CF)

Ghrelin levels

Patients presenting clinical success and clinical failure showed similar levels (p=0.32) and behavior over time (p=0.44). There was a statistically significant variation of ghrelin levels within groups throughout the assessments (p=0.02) but no statistical difference between baseline and 12 months measures. For both groups, there was a decrease between 0 and 30min (p=0.003) and times 0 and 60min (p=0.01) at baseline. However, at 12 months, a statistically significant reduction in ghrelin levels was delayed and occurred between 0 and 60min (p=0.005) and 0 and 90min (p=0.009). Table 3 summarizes ghrelin levels as it pertains to CS.

Concerning the AUC between times 0 and 30min, the values were similar (p=0.74) between CS and CF groups at baseline (619 ± 340 vs. 596 ± 396) and 12 months (611 ± 329 vs. 753 ± 1,048). There was no statistically significant change in the AUC from baseline to follow-up (p=0.89).

GLP-1 levels

Patients presenting clinical success and clinical failure showed similar levels (p=0.53) and behavior over time (p=0.83). There was a statistically significant variation of GLP-1 levels within groups throughout the assessments (p<0.001), and all baseline values are statistically higher than the follow-up ones (p<0.001). For both groups, there was an increase in GLP-1 levels from time 0 to all other assessments at baseline and 12 months (Table 3).

As to the AUC between 30 and 120 minutes, patients from both groups presented similar means (p=0.63) at baseline and follow-up. Both CS and CF groups showed a statistically significant reduction in the AUC from preprocedural to 12 months (2,951 ± 1,527 vs. 1,385 ± 788, p<0.001; and 3,028 ± 1,881 vs. 2,046 ± 1,999, p<0.001, respectively).

PYY levels

Patients presenting clinical success and clinical failure showed similar levels (p=0.32) and behavior over time (p=0.44). There was a statistically significant variation of PYY levels within groups throughout the assessments (p<0.001) due to an increase from time 0 to all other time points (p<0.001) at baseline and follow-up (Table 3).

Regarding the AUC between 30 and 120 minutes, patients from both groups presented similar means at baseline and follow-up (p=0.32). For both CS and CF patients, there was no statistically significant change between preprocedural to 12 months values (16,176 ± 7,551 *vs.* 18,363 ±8,527.3 and 14,664 ± 7,410 *vs*. 15,332 ± 6,928, p=0.23, respectively).

TABLE 3

Post-hoc analysis (cholecystectomized vs. non-cholecystectomized)

Ghrelin levels and dynamics did not differ significantly between groups. GLP-1 levels reduced at follow-up compared to baseline in both cholecystectomized and non-cholecystectomized individuals. As to PYY, non-cholecystectomized patients presented a non-significant decrease in PYY levels from baseline to 12 months, while cholecystectomized individuals' levels had a non-significant increase. Therefore, as these changes were in opposite direction, cholecystectomized patients had a statistically significant higher AUC at follow-up. The complete results from the post-hoc analysis are available in the Supplementary Material.

Discussion

This is the first study assessing the dynamics of gut hormones after TORe in post-RYGB patients. We demonstrated that the endoscopic treatment addressing the stoma dilation elicits significant enterohormonal changes, which is more pronounced in cholecystectomized individuals and those undergoing APC-TORe.

For almost two decades, several endoscopic techniques addressing stoma dilation have been employed to address significant weight regain after surgery. [5,12] Although clinical data on TORe is abundant, few data on its physiology currently exist. [16] Among the appetite-regulating hormones, ghrelin is the most widely studied and it is considered the most influential in dictating the level of fasting hunger. [11,17] Therefore, it plays a critical pre-meal role but exerts little action after food intake distends the stomach and inhibits P/D1 cells. [18] On the other hand, small and large-bowel cells produce and release PYY and GLP-1 hormones once the food bolus reaches the intestinal lumen. Consequently, they play a later role in appetite regulation through gut-brain (triggering satiation and meal termination) and gut-gut communication (downregulating gastrointestinal peristalsis and inducing satiety). [19] Their effect is noteworthy as inhibiting their action leads to decreased appetite and food intake, which rendered PYY and GLP-1 the main targets of new weight loss medications. [19,20] This background explains why we selected ghrelin, GLP-1, and PYY for the present study. Also, it supports the rationale for investigating the AUC between times 0-30min for ghrelin and AUC between 30-120min for GLP-1 and PYY.

Ghrelin is arguably the most essential hunger-mediating hormone. In our study, stoma reduction did not significantly alter ghrelin levels. Instead, it delayed the decrease in ghrelin levels, which is similar at baseline and follow-up, relocating the nadir level from the 30-60 minutes to the 60-90 minutes interval. All analyses presented this same pattern, increasing reliability in the results but showing no correlation with the type of procedure (APC or APC plus suture) or history of cholecystectomy. Of note, patients with ≥10%TBWL at 12 months had similar values and changes to those with <10%TWL. The absence of significant changes in the AUCs of ghrelin levels also corroborates that. Therefore, it seems that ghrelin response is unrelated to clinical success, and no specific baseline behavior or cut-off threshold can be used as a predictor of better response to TORe. [21,22]

Our study demonstrated that one year after TORe, patients experienced an overall decrease in GLP-1 levels. This finding was constant, regardless of allocation group, clinical success, or history of cholecystectomy. The AUC between postprandial 30 and 120 minutes decreased accordingly. The most traditional and primary rationale for reducing the stoma size is improving food retention in the gastric pouch, delaying emptying, and augmenting its postprandial distention. Vagal neural efferents communicate with the CNS, inducing satiety and

meal termination. Also, with a reduced outlet, the food bolus leaves the pouch at a more controlled pace, [8] which justifies the reduction in GLP-1 levels after TORe. Considering the critical incretin effect of GLP-1, one should expect worsening of metabolic diseases. Interestingly, sound data shows an actual improvement in lipid panel and glycemic parameters after TORe, contradicting such expectation. [5,12] The concurrent weight loss and other still unclear factors probably outclass such negative aspects and explain why clinical improvement is so extensively reported in this context. [22–24]

The documented change in PYY levels and dynamics is the most remarkable finding in our study. First, we found no difference when comparing patients achieving ≥10%TWL to those with <10%TBWL. That applies to both baseline and follow-up assessments. Ultimately, it seems that no specific pattern or values of PYY can be used to predict clinical success and that there is no typical pattern to characterize successful cases at one year. However, PYY levels and dynamics were distinctively different when we compared cohorts according to allocation group and history of cholecystectomy.

Regarding the history of cholecystectomy, we initially found significantly higher PYY values in the cholecystectomized cohort, which applies to baseline and follow-up assessments. That is a novel and exciting finding. The physiological relationship between the gallbladder and PYY is not well-established. We speculate this interaction could be related with the Fibroblast Growth Factor 19 (FGF-19). Ileal enterocytes are mainly responsible for secreting FGF-19 in response to bile acid activation of their nuclear receptor FXR. [13,14] Then, the FGF-19 acts on hepatic receptors to limit bile acid synthesis as negative feedback. Recent data also indicate that FGF-19 helps regulate glucose homeostasis and energy metabolism. [25] Since PYY and GLP-1 secretions are also mediated by bile acids concentration, FGF-19 could indirectly downregulate them. In patients with intact biliopancreatic anatomy, FGF-19 simultaneously inhibits bile acid production in the liver and stimulates gallbladder filling. [14] For cholecystectomized individuals, we hypothesize that the bile that would once be directed to the gallbladder ends up in the duodenum and towards the common limb. That could increase luminal bile acid availability compared to a non-cholecystectomized counterpart and explain the higher PYY baseline values in this subset of patients. Remarkably, GLP-1 levels did not follow the same pattern, ultimately suggesting a more complex and unexplored pathway in its regulation.

In addition, cholecystectomized individuals experienced an increase in the AUC of PYY between 30 and 120 minutes, while non-cholecystectomized ones had a non-significant decrease. That explains the behavioral difference in PYY dynamics between groups and lays the groundwork for the significant difference in the mean AUC at 12 months. We detected similar findings by dichotomizing the sample according to allocation group, with higher values in the APC group. One could argue that either the history of cholecystectomy or the allocation group could be a confounder variable toward the change in AUC. To address such concern, we ran two additional statistical tests (chi-square and two-factor variance analysis) to assess for an association between those two variables, but they were both negative. Eventually, a positive history of cholecystectomy and APC-TORe allocation seem to synergistically and independently contribute to the increase in PYY levels.

This increase may look illogical as opposed to the simultaneous GLP-1 decrease. Since PYY and GLP-1 are typically co-secreted by the same ileal cells in a normal situation, one should expect similar behaviors. We speculate that this finding may be related to cell repopulation or a shift in gene expression following an aggressive thermal injury. Changes in the density and distribution of gut endocrine cells have already been documented after uneventful bariatric surgery. [26] Moreover, mucosal thermal injury has been extensively used to induce cell repopulation. Examples include endoscopic treatment of Barrett's esophagus using APC [27] or cryoablation [28] and duodenal mucosal resurfacing to treat type 2 diabetes. [29] Of note, interesting cases of complete squamous metaplasia of the gastric pouch following APC-TORe have also been reported. [30] It is possible, then, that the more aggressive thermal injury during the APC-TORe with repeated sessions, as opposed to Sutured-TORe, could trigger an increase in PYY-specialized enteroendocrine cells or enhance PYY gene expression. That could explain the difference between groups and why there is an independent secretion of PYY and GLP-1 after APC-TORe.

Our study is not free from limitations. First, we have a small sample size since it derives from a pilot clinical trial. However, physiology studies on documented clinical outcomes rarely include large samples. [24,25] Such studies are time-consuming and expensive, and few patients voluntarily agree to participate as personal benefits are minimal. In addition, we need histological evaluation to corroborate our hypothesis on cell repopulation. Further studies could efficiently address this gap by collecting biopsies from the distal gastric pouch, the anastomosis,

and the proximal jejunum at baseline and follow-up. In this sense, gastric emptying tests could have added valuable information to corroborate our findings with respective explanations. Again, this seems an exciting opportunity for further research. Finally, one should interpret our results with caution as weight loss itself, despite anatomical changes, could be responsible for driving hormonal levels up or down.

In conclusion, our findings collectively suggest that TORe triggers a significant enteroendocrine response, which is different in APC-TORe and Sutured-TORe patients. Cholecystectomized patients have more pronounced changes in PYY levels and GLP-1 levels decrease after TORe, despite the technique employed.

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Supplementary material

Gut hormones assessment

At the time of the quantification, the frozen plasma samples were defrosted and centrifuged at 4500rpm at room temperature for five minutes. Plasma specimens were prepared for analysis in a 96-well plate utilizing a Human Metabolic Hormone Magnetic Bead Panel (Millipore Corp., Billerica, MA, USA) per the manufacturer's kit-specific protocols. Analytes were quantified using a Magpix analytical test instrument, which utilizes xMAP technology, multiple analyte profiling (Luminex Corporation, Austin, TX, USA), and xPONENT 4.2 software (Luminex). xMAP technology uses fluorescent-coded color magnetic microspheres coated with analyte-specific capture antibodies to simultaneously measure multiple analytes in a single specimen. After the micro-spheres have captured the analytes, a biotinylated detection antibody binds to that complex. Streptavidin PE then attaches as a reporter molecule. Inside the instrument, magnetic beads are held in a monolayer by a magnet. Two LEDs are used to excite the internal micro-sphere dye and the dye of the reporter molecule, respectively. A CCD camera captures these images, which are then analyzed by the Milliplex Analyst 5.1 software (Millipore Corporation, Billerica, MA, USA). Concentrations of hormones in pg/mL were determined based on the fit of a standard curve for mean fluorescence intensity. All assessments were conducted on the same day to avoid time-related interference in the results.

Post-hoc analysis (cholecystectomized vs. non-cholecystectomized)

Ghrelin

Patients with and without a history of cholecystectomy presented similar means (p=0.49) and behavior over time (p=0.89). There was a significant variation of ghrelin levels within groups throughout the assessments (p=0.02) but no statistical difference between baseline and 12 months measures. For both groups, there was a decrease between 0 and 30min (p=0.002) and 0 and 60min (p=0.01) at baseline. However, at 12 months, a significant reduction in ghrelin levels was delayed and occurred between 0 and 60min (p=0.006) and 0 and 90min (p=0.01). Table 1 Suppl summarizes ghrelin levels as it pertains to the history of cholecystectomy.

Concerning the area under the curve between times 0 and 30min, the means were similar (p=0.94) between cholecystectomized and non-cholecystectomized patients at baseline (641.6 $\pm$ 445.2 vs. 591.6 $\pm$ 329.6) and 12 months (634.7 $\pm$ 387.9 vs. 752.7 $\pm$ 1,061.4). There was no significant change in the area under the curve from baseline to follow-up (p=0.88).

GLP-1

Patients with and without a history of cholecystectomy presented similar means (p=0.63) and behavior over time (p=0.53). There was a significant variation of GLP-1 levels within groups throughout the assessments (p<0.001), and all baseline values are statistically higher than the 12 months measures (t0: p=0.002; t30, t60, t90: p<0.001; t120: p=0.003). For both groups,

there was an increase in GLP-1 levels from time 0 to all other assessments at baseline and follow-up (Table 1 Suppl).

As to the area under the curve between 30 and 120 minutes, patients from both groups presented similar means (p=0.44) at baseline and follow-up. Both cholecystectomized and non-cholecystectomized patients presented a significant reduction in the area under the curve from preprocedural to 12 months (3,171.9 ± 1,798.8 *vs*. 2,053.5 ± 2,153.7 p<0.001; and 2,858.4 ± 1,754.5 *vs*. 1,397.1 ± 729.9, p<0.001, respectively).

PYY

Patients with and without a history of cholecystectomy presented similar behavior over time (p=0.11). However, cholecystectomized patients showed significantly higher mean levels of PYY throughout time (p=0.01). In addition, there was a significant variation of PYY levels within groups throughout the assessments (p<0.001) due to an increase from time 0 to all other time points (p<0.001) at baseline and follow-up (Table 1 Suppl).

Regarding the area under the curve between 30 and 120 minutes, non-cholecystectomized and cholecystectomized patients presented similar means at baseline (14,048.5 ± 6,410 *vs*. 17,016.5 ± 8,848.7, p=0.25), but the latter group had higher values at 12 months (13,177.2 ± 5,825.3 *vs*. 21,461.6 ± 7,728.1, p=0.001). There was no statistical difference between baseline and follow-up values within groups (p=0.41 non-cholecystectomized and p=0.07 for cholecystectomized). Non-cholecystectomized patients presented a non-significant decrease in PYY levels from baseline to 12 months, while cholecystectomized individuals' levels increased significantly. Therefore, there was a difference in behavior over time (p=0.02), leading to a statistical difference at follow-up.

Using the chi-square test, we found no significant association between the allocation group and the history of cholecystectomy (p=0.053). Similarly, there was no association between clinical success and a history of cholecystectomy (p= 0.67). The variation of PYY within groups (delta = 12 months PYY - baseline PYY) presents normal distribution, which allowed for a two-factor variance analysis. This further statistical analysis aligns with the chi-square test to identify an interaction between two variables toward the same outcome. The two-factor variance analysis confirmed no association between the allocation group and the history of cholecystectomy (p= 0.93). Ultimately, both factors influence the delta in PYY levels independently.

TABLE 1 (suppl)

Table 1 (suppl) - Summary of gut hormone levels in pg/mL according to the history of cholecystectomy and assessment times. Min: minutes; n = sample size; APC: argon plasma coagulation

Ghrelin	
	Cholecystectomy

	Time (min)	No (n=22)			Yes (n=14)		
Baseline	0	23.5	±	17.1	26.2	±	23.4
	30	15.9	±	9.8	16.5	±	9.4
	60	15.7	±	7.2	18.1	±	8.2
	90	19.2	±	13.5	18.1	±	6.9
	120	25.5	±	28.2	33.8	±	37.3
12 months	0	19.7	±	10.9	25.4	±	19
	30	30.4	±	63.7	16.8	±	7.8
	60	15	±	6.3	15.9	±	6.4
	90	14.6	±	6.7	17.8	±	9.4
	120	18.2	±	11.7	25.6	±	19.8

GLP-1

	Time (min)	No (n=22)			Yes (n=14)		
Baseline	0	12.1	±	7.7	15.3	±	15.6
	30	40.5	±	37.4	30.6	±	16
	60	27.6	±	14.1	36.4	±	37.2
	90	30.1	±	26.1	36.2	±	34.3
	120	34.5	±	46	35.4	±	49.7
12 months	0	8.2	±	10.8	13	±	25.7
	30	16.8	±	10	26.3	±	25.7
	60	14.3	±	6.5	24.2	±	25.9
	90	17.3	±	15.9	20.1	±	23.1
	120	13	±	8.6	21.8	±	22.7

PYY

	Time (min)	No (n=22)			Yes (n=14)		
Baseline	0	67.6	±	60.2	90.2	±	78
	30	270.9	±	146.3	268.1	±	113.1
	60	158.9	±	69.3	197.8	±	94.8
	90	111.1	±	56.6	148.5	±	109.9
	120	125.4	±	126.3	173.6	±	131.1
12 months	0	62.6	±	61.7	100.8	±	80.4
	30	277.1	±	157	353.9	±	156.5
	60	147	±	69.3	233.8	±	87.6

90	105.5	±	57.3	213.6	±	74.6
120	96	±	51.5	181.8	±	96.6

Table 1 – Baseline characteristics for the patients included in the present study.

		Allocation group		
	Total (n=36)	**APC (n=19)**	**APC + Suture (n=17)**	**p-value***
Age (years)	44.9 ± 10.6	45.6 ± 10.7	44.1 ± 10.7	0.67
Years after surgery (years)	7.8 ± 4.5	8.5 ± 4.9	7.0 ± 3.9	0.31
Height (cm)	164.4 ± 9.1	163.2 ± 9.8	165.8 ± 8.5	0.41
Pre-operative weight (kg)	140.0 ± 41.0	128.9 ± 31.1	152.4 ± 47.6	0.08
Pre-operative BMI (kg/m^2)	51.3 ± 11.5	48.0 ± 8.7	54.9 ± 13.2	0.07
Pre-operative EW (kg)	72.2 ± 36.8	62.0 ± 26.3	83.5 ± 44.0	0.09
Nadir Weight (kg)	90.1 ± 28.5	84.2 ± 20.7	96.7 ± 34.8	0.20
Excess Weight Loss at Nadir (%)	73.8 ± 19.1	75.0 ± 19.5	72.4 ± 19.2	0.69
Pre-revisional Weight (kg)	115.6 ± 30.1	110.4 ± 25.7	121.4 ± 34.2	0.27
Pre-revisional BMI (kg/m^2)	42.4 ± 7.9	41.0 ± 5.8	43.9 ± 9.7	0.29
Endoscopic Pouch Length (cm)	4.9 ± 1.4	4.7 ± 1.3	5.1 ± 1.5	0.43
Endoscopic Anastomosis Diameter (mm)	21.1 ± 5.8	20.3 ± 5.9	22.1 ± 5.8	0.37

	Clinical Success (≥10%TWL at 12 months)		
	Yes (14)	No (22)	
Age (years)	47.36 ± 12.3	43.4 ± 9.3	0.28
Years after surgery (years)	8.29 ± 5.4	7.5 ± 3.9	0.61
Height (cm)	163 ± 9.1	165.4 ± 9.3	0.45
Pre-operative weight (kg)	140.9 ± 23.2	139.4 ± 49.6	0.90
Pre-operative BMI (kg/m^2)	53.3 ± 9.3	50 ± 12.7	0.41
Pre-operative EW (kg)	74.3 ± 23	70.8 ± 43.9	0.76
Nadir Weight (kg)	85.1 ± 12.4	93.3 ± 35.1	0.32
Excess Weight Loss at Nadir (%)	76.1 ± 14.8	72.3 ± 21.6	0.56
Pre-revisional Weight (kg)	111.2 ± 18.1	118.5 ± 35.8	0.42
Pre-revisional BMI (kg/m^2)	42 ± 7	42.6 ± 8.6	0.83
Endoscopic Pouch Length (cm)	5.1 ± 1.7	4.7 ± 1.2	0.46
Endoscopic Anastomosis Diameter (mm)	21.9 ± 5.3	20.7 ± 6.3	0.55

	Cholecystectomy		
	Yes (14)	No (22)	
Age (years)	47.7 ± 11.7	42.4 ± 9.2	0.15
Years after surgery (years)	9.1 ± 5.8	6.9 ± 3.3	0.21
Height (cm)	162.6 ± 9	166.1 ± 9.2	0.28
Pre-operative weight (kg)	135.6 ± 29.6	144.8 ± 47.4	0.52
Pre-operative BMI (kg/m^2)	51.2 ± 9.6	51.9 ± 12.8	0.86
Pre-operative EW (kg)	69.3 ± 26.4	75.7 ± 43	0.62
Nadir Weight (kg)	87 ± 20.4	92.8 ± 33.7	0.56
Excess Weight Loss at Nadir (%)	71.7 ± 14.7	76 ± 21.9	0.52
Pre-revisional Weight (kg)	110.5 ± 25.3	119.5 ± 33.65	0.39
Pre-revisional BMI (kg/m^2)	41.5 ± 6.5	42.9 ± 9	0.61

Endoscopic Pouch Length (cm)	5 ± 1.8	4.9 ± 1.2	0.85
Endoscopic Anastomosis Diameter (mm)	20.1 ± 7.2	22 ± 4.9	0.36

(*) Student/s t-test

Table 2 – Summary of gut hormone levels in pg/mL according to allocation group and assessment times. Min: minutes; n = sample size; APC: argon plasma coagulation

	Time (min)	Sample (n=36)	APC (n=19)			APC + Suture (n=17)		
Ghrelin								
Baseline	0	24.3 ± 19.4	28	±	23.8	20.1	±	12.2
	30	16.0 ± 9.4	18.3	±	12.1	13.5	±	3.9
	60	16.5 ± 7.5	16.4	±	7.3	16.6	±	8
	90	18.7 ± 11.0	21.5	±	14.3	15.6	±	4.3
	120	28.8 ± 31.4	33.1	±	36.1	24	±	25.5
12 months	0	21.8 ± 14.5	24.9	±	15.5	18.4	±	13
	30	24.6 ± 48.8	34.6	±	66.2	13.6	±	6.6
	60	15.3 ± 6.2	15.7	±	5.9	14.8	±	6.7
	90	16.0 ± 7.9	16.3	±	7.9	15.7	±	8.2
	120	21.2 ± 15.4	24.9	±	15.1	17	±	15
GLP-1								
Baseline	0	13.5 ± 11.2	16.9	±	13.4	9.6	±	6.8
	30	39.8 ± 30.4	42	±	39.5	31.1	±	14.1
	60	31.3 ± 25.5	34.8	±	33.1	27.3	±	12.3
	90	32.7 ± 28.9	37	±	30.9	27.9	±	26.5
	120	34.9 ± 46.1	39.4	±	48.7	29.8	±	44
12 months	0	10 ± 17.8	12.4	±	22.1	7.4	±	11.4
	30	21.2 ± 18.4	24.4	±	22.3	17.7	±	12.5
	60	21.3 ± 25.3	26	±	33.4	16.1	±	9.5
	90	19.1 ± 19.0	23.7	±	24.5	14	±	7.9
	120	17 ± 16.1	20.3	±	19.5	13.2	±	10.6
PYY								
Baseline	0	76.7 ± 66.7	104.3	±	78	45.8	±	31.2
	30	268.5 ± 130.6	259.5	±	121.1	278.5	±	143.5
	60	174 ± 80.3	181	±	84.6	166.1	±	77.1
	90	127.3 ± 81.9	131	±	76.1	123.2	±	90.2
	120	145.5 ± 126.8	178.8	±	138.7	108.3	±	103.6
12 months	0	77.3 ± 70.3	110.2	±	80	40.5	±	29.7
	30	310.4 ± 157.6	344	±	173.8	272.9	±	132.3
	60	180.1 ± 86.8	206.4	±	92	150.7	±	71.9
	90	149.2 ± 82.2	185.5	±	87	108.7	±	54.3
	120	131.5 ± 82.2	173.5	±	88.6	84.6	±	40

Table 3 – Summary of gut hormone levels in pg/mL according to clinical success and assessment times. Min: minutes; n = sample size; APC: argon plasma coagulation

		Clinical Success					
Ghrelin							
	Time (min)	No (n=22)			Yes (n=14)		
Baseline	0	25.6	±	23.2	22.2	±	11.6
	30 min	14.1	±	5.2	19	±	13.3
	60 min	14.8	±	6.6	19.1	±	8.4
	90 min	17.6	±	7.9	20.6	±	14.8
	120 min	26.1	±	25.1	32.9	±	40.1
12 months	0	20.2	±	13.5	24.4	±	16.2
	30 min	29.9	±	62.2	16.3	±	7.3
	60 min	14.6	±	6.2	16.3	±	6.3
	90 min	16.1	±	8.8	15.8	±	6.6
	120 min	18.7	±	15.1	25	±	15.5
GLP-1							
	Time (min)	No (n=22)			Yes (n=14)		
Baseline	0	15.1	±	13.3	10.9	±	6.6
	30	38.6	±	35.4	34.1	±	21.1
	60	32.7	±	30.7	29	±	14.6
	90	33.1	±	31.3	32	±	25.9
	120	31.4	±	39.7	40.3	±	55.9
12 months	0	11.8	±	20.7	7.3	±	12.2
	30	24.6	±	22.1	16	±	8.4
	60	25.5	±	31.2	14.7	±	8.4
	90	21.2	±	21.7	15.9	±	14
	120	18.3	±	19.4	14.9	±	9
PYY							
	Time (min)	No (n=22)			Yes (n=14)		
Baseline	0	62.7	±	41	98.6	±	91.7
	30	253.1	±	122	292.6	±	143
	60	160.2	±	73	195.6	±	89.1
	90	123	±	85	134.2	±	79.6
	120	157.9	±	144.3	126	±	94.8
12 months	0	66.5	±	53.9	94.3	±	90
	30	285.4	±	123.4	349.6	±	198.8
	60	168.1	±	80.8	198.9	±	95.1
	90	137.4	±	83.8	167.8	±	79
	120	125.6	±	85.4	140.9	±	79.7