Endoscopic transoral outlet reduction induces enterohormonal changes in patients with weight regain after Roux-en-Y gastric bypass

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Authors

Vitor Ottoboni Brunaldi[1], Galileu Ferreira Farias[2], Diogo Turiani Hourneaux de Moura[1], Marco Aurélio Santo[3], Barham K. Abu Dayyeh[4], Caroline Silverio Faria[5], Leila Antonangelo[6], Dan Linetzki Waitzberg[7], Eduardo Guimarães Hourneaux de Moura[8]

Institutions

1 Gastrointestinal Endoscopy Unit, Gastroenterology Department, Universidade de Sao Paulo Faculdade de Medicina, Sao Paulo, Brazil
2 General Surgery, Universidade de Sao Paulo Faculdade de Medicina, Sao Paulo, Brazil
3 Bariatric Surgery Unit, Gastroenterology Department, Universidade de Sao Paulo Faculdade de Medicina, Sao Paulo, Brazil
4 Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, United States
5 Lim03, Universidade de Sao Paulo Faculdade de Medicina, Sao Paulo, Brazil
6 Pathology Department, Universidade de Sao Paulo Faculdade de Medicina, Sao Paulo, Brazil
7 Gastroenterology Department, Universidade de Sao Paulo Faculdade de Medicina, Sao Paulo, Brazil
8 Gastrointestinal Endoscopy Department, Universidade de Sao Paulo Hospital das Clinicas, Sao Paulo, Brazil

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70469 Stuttgart, Germany

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Corresponding author

Dr. Vitor Ottoboni Brunaldi, MD, MSc, Universidade de Sao Paulo Faculdade de Medicina, Gastrointestinal Endoscopy Unit, Gastroenterology Department, Eneas de Carvalho Aguiar Av. 255, 05403-000 Sao Paulo, Brazil
vbrunaldi@gmail.com

ABSTRACT

Background and study 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 was 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 the APC-suture group did not. Naïve patients had significantly lower PYY levels at baseline ($P=0.01$) compared with cholecystectomized individuals. This latter group experienced a significant increase in area under the curve (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.

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].

Because 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 transoral outlet reduction (TORe) with endoscopic suturing or argon plasma coagulation (APC) alone [5]. Several studies report favorable weight loss and resolution of comorbidities, but few have investigated the underlying physiology [6, 7]. Some preliminary data suggest that 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 ones most often implicated 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 hormone dynamics after TORe could help create more thorough bariatric approaches. Therefore, the present study was designed to help elucidate part of the physiological pathway through which weight loss occurs after revision of gastrojejunostomy.

Patients and methods

Design and registry

This was a branch of a previous single-center, pilot randomized trial with clinical results published elsewhere [12]. It was registered in Clinicaltrials.gov (NCT03094936) and had Investigational Review Board approval (Protocol number 1.857.932/2016).

Population

Adult patients (aged 18–60 years) with significant weight regain after RYGB (> 20% from nadir weight) and dilated gastrojejunal anastomosis (≥ 15 mm) were randomly assigned to TORe with APC alone or APC plus endoscopic suturing with the Apollo Overstitch device (Apollo Endosurgery, Austin, Texas, United States). 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 who were pregnant, had coagulopathy, moderate and severe erosive esophagitis, and who were concurrently using anorexigenic drugs were excluded from the trial. All information about settings, endoscopic procedures, and follow-up strategy is 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 1 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 percentage of total weight loss (%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). Because 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. Because 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

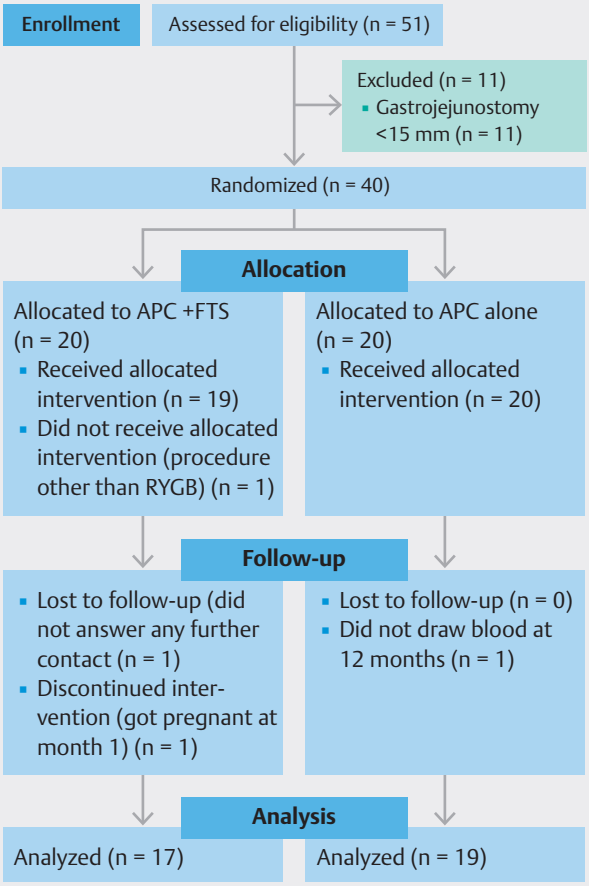
After the trial was designed, some articles described an exciting interaction between the gallbladder and the gut hormones responsible for mediating satiety, satiation, and gastrointestinal motility [13, 14]. Therefore, we planned a post-hoc analysis to compare the levels and dynamics of ghrelin, GLP-1,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

Blood draw protocol

Patients were instructed about 12-hour fasting prior to assessment of gut hormones. 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 4500 rpm at 4°C, divided into 1.5-mL aliquots, and then frozen at −20°C until all blood samples (baseline and follow-up) were available for assessment of gut hormones. [15]. The descriptive protocol for gut hormones assessment is available in **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's *t*-test to compare continuous variables. The analysis of variance for repeated measures (ANOVA test) was used to analyze and compare variation in hormone 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, New York, United States). $P<0.05$ was considered statistically significant for a 95% confidence interval.



▶ **Fig. 1** Inclusion flowchart.

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 (▶ **Fig. 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.

APC vs. APC + Suture

Ghrelin levels

The allocation groups had similar hormone levels at the different 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 30 minutes ($P=0.001$) and from 0 to 60 minutes ($P=0.005$). At 12 months, the decrease was delayed and occurred between 0 and 60 minutes ($P=0.006$) and between times 0 and 90 minutes ($P=0.013$). ▶ **Table 2** summarizes the ghrelin levels according to group and assessment times, and the comparisons between times of assessment for both groups. ▶ **Fig. 2** depicts the behavior of ghrelin levels over time.

The AUC between times 0 and 30 minutes 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 no difference in behavior over time ($P=0.43$) or statistically significant change between baseline and 12 months within the same allocation group.

GLP-1 levels

The allocation groups had similar hormone levels at the different 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 time 0 to the other assessments (▶ **Table 2, Fig. 2**).

Concerning the AUC between times 30 and 120 minutes, the means were similar ($P=0.15$) between the 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 had a statis-

▶ **Table 1** Baseline characteristics of patients included in the 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
Preoperative weight (kg)	140.0 ± 41.0	128.9 ± 31.1	152.4 ± 47.6	0.08
Preoperative BMI (kg/m^2)	51.3 ± 11.5	48.0 ± 8.7	54.9 ± 13.2	0.07
Preoperative 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
Preoperative weight (kg)		140.9 ± 23.2	139.4 ± 49.6	0.90
Preoperative BMI (kg/m^2)		53.3 ± 9.3	50 ± 12.7	0.41
Preoperative 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
Preoperative weight (kg)		135.6 ± 29.6	144.8 ± 47.4	0.52
Preoperative BMI (kg/m^2)		51.2 ± 9.6	51.9 ± 12.8	0.86
Preoperative 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.
APC, argon plasma coagulation; BMI, body mass index; EW, estimated weight; TWL, total weight loss.

▶ **Table 2** Summary of gut hormone levels in pg/mL according to allocation group and assessment times.

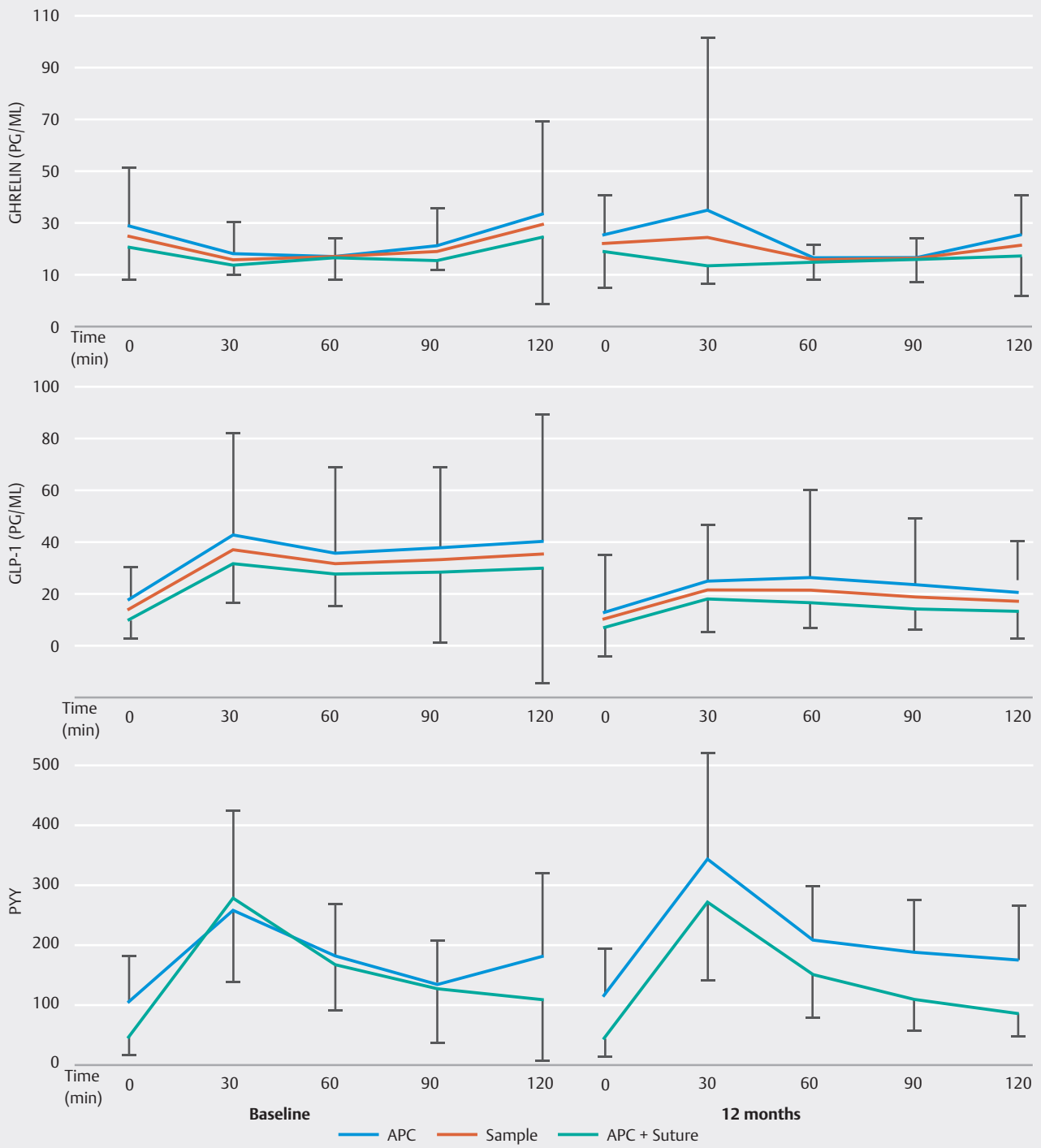
	Time (min)	Sample (n = 36)	APC (n = 19)	APC + suture (n = 17)
Ghrelin				
Baseline	0	24.3 ± 19.4	28 ± 23.8	20.1 ± 12.2
	30	16.0 ± 9.4	18.3 ± 12.1	13.5 ± 3.9
	60	16.5 ± 7.5	16.4 ± 7.3	16.6 ± 8
	90	18.7 ± 11.0	21.5 ± 14.3	15.6 ± 4.3
	120	28.8 ± 31.4	33.1 ± 36.1	24 ± 25.5
12 months	0	21.8 ± 14.5	24.9 ± 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

APC, argon plasma coagulation; GLP-1, glucagon-like peptide 1; PYY, peptide YY.

tically significant decrease in AUC between 30 and 120 minutes from baseline to 12 months (P<0.001). Nonetheless, the decrease was similar between groups (P = 0.64).

PYY levels

The allocation groups had 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



▶ **Fig. 2** Graph showing gut hormone levels for each allocation group over time.

and 12-month levels, except for a statistically significant increase at 90 minutes (131 ± 76.1 *vs.* 185.5 ± 87, *P* = 0.017). Patients in the APC + suture group experienced no difference in preprocedure versus follow-up PYY levels at any of the 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, Fig. 2**).

The groups had different trends concerning AUC between 30 and 120 minutes (*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 had a non-significant decrease (14,486 ± 7,597 vs. 13,146 ± 5,767, *P* = 0.41).

▶ **Table 3** Summary of gut hormone levels in pg/mL according to clinical success and assessment times.

	Time (min)	No (n = 22)	Yes (n = 14)
Ghrelin			
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			
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			
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

Clinical success vs. clinical failure

Ghrelin levels

Patients with clinical success (CS) and clinical failure (CF) showed similar hormone levels ($P = 0.32$) and behavior over time ($P = 0.44$). There was a statistically significant variation in ghrelin levels within groups throughout the assessments ($P = 0.02$) but no statistical difference between the baseline and 12-months measurements. For both groups, there was a decrease between 0 and 30 minutes ($P = 0.003$) and times 0 and 60 minutes ($P = 0.01$) at baseline. However, at 12 months, a statistically significant reduction in ghrelin levels was delayed and occurred between 0 and 60 minutes ($P = 0.005$) and 0 and 90 minutes ($P = 0.009$). ▶ **Table 3** summarizes ghrelin levels as they pertain to CS.

Concerning the AUC between times 0 and 30 minutes, the values were similar ($P = 0.74$) between the 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 with CS and CF had similar levels ($P = 0.53$) and behavior over time ($P = 0.83$). There was a statistically significant variation in GLP-1 levels within groups throughout the assessments ($P<0.001$), and all baseline values were statistically higher than those for follow-up ($P<0.001$). 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 for the AUC between 30 and 120 minutes, patients from both groups had similar means ($P = 0.63$) at baseline and follow-up. Both the CS and CF groups had a statistically significant reduction in AUC from pre-procedure 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 with CS and CF had similar hormone levels ($P = 0.32$) and behavior over time ($P = 0.44$). There was a statistically significant variation in 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 had similar means at baseline and follow-up ($P = 0.32$). For both patients with CS and CF, there was no statistically significant change between pre-procedure and 12-month 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).

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

Ghrelin levels and dynamics did not differ significantly between groups. GLP-1 levels were lower at follow-up compared with baseline in both cholecystectomized and non-cholecystectomized individuals. As to PYY, non-cholecystectomized patients had a non-significant decrease in PYY levels from baseline to 12 months, whereas levels in cholecystectomized individuals had a non-significant increase. Therefore, because these changes were in opposite directions, 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 was the first study to assess the dynamics of gut hormones after TORe in post-RYGB patients. We demonstrated that endoscopic treatment addressing the stoma dilation elicits significant enterohormonal changes, which are 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 are abundant, few data current exist about its physiology [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 because inhibiting their action leads to decreased appetite and food intake, which have 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 to 30 minutes for ghrelin and AUC between 30 and 120 minutes 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- to 60-minute interval to the 60- to 90-minute interval. All analyses had 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% total body weight loss (TBWL) at 12 months had values and changes similar 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 CS 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 1 year after TORe, patients experienced an overall decrease in GLP-1 levels. This finding was constant, regardless of allocation group, CS, 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 central nervous system, 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 show 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, 23, 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 CS and that there is no typical pattern to characterize successful cases at 1 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 applied to baseline and follow-up assessments. That was a novel and exciting finding. The physiological relationship between the gallbladder and PYY is not well-established. We speculate this interaction could be related to 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]. Because PYY and GLP-1 secretion also is mediated by bile acid 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 toward the common limb. That could increase luminal bile acid availability compared with 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 AUC of PYY between 30 and 120 minutes, while non-cholecystectomized individuals had a non-significant decrease. That explains the behavioral difference in PYY dynamics between groups and lays the groundwork for the significant difference in 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 confounding variable affecting change in AUC. To address such a concern, we ran two additional statistical tests (chi-square and two-factor variance analysis) to assess for an association between those two variables, but the results were negative. Eventually, a positive history of cholecystectomy

and APC-TORe allocation seem to synergistically and independently contribute to an increase in PYY levels.

This increase may look illogical as opposed to the simultaneous GLP-1 decrease. Because 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 independent secretion of PYY and GLP-1 after APC-TORe.

Our study is not free from limitations. First, we had a small sample size because it derived from a pilot clinical trial. However, physiology studies about documented clinical outcomes rarely include large samples [24, 25]. Such studies are time-consuming and expensive, and few patients voluntarily agree to participate because the 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 because weight loss itself, despite anatomical changes, could be responsible for driving hormone levels up or down.

Conclusions

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.

Conflict of Interest

VOB: none. GFAF: none. DTHM: Advisory board of Bariatec Advanced Solutions. MAS: none. BKAD: Consultant for Metamodix, BFKW, DyaMx, Boston Scientific, USGI Medical, and Endo-TAGSS; gets research support from Boston Scientific, USGI Medical, Apollo Endosurgery, Spatz Medical, GI Dynamics, Cairn Diagnostics, Aspire Bariatrics, and Medtronic; is speaker for Johnson and Johnson, Endogastric Solutions, and Olympus. CSF: none. LA: none. DLW: none. EGHM: Speaker for Boston Scientific and Olympus.

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