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Gastrojejunal Anastomotic Reduction for Weight Regain in Roux-en-Y Gastric Bypass Patients: Physiological, Behavioral and Anatomical Effects of Endoscopic Suturing and Sclerotherapy

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Abstract

Background—Weight regain is common after Roux-en-Y gastric bypass (RYGB).

Objectives—To assess the mechanisms of weight loss after two Gastrojejunal Anastomotic Reduction (GJAR) procedures to treat weight regain.

Setting—University Hospital, United States

Methods—43 RYGB patients with weight regain were prospectively enrolled. Weight, ghrelin levels, responses to the 21-item Three-Factor Eating Questionnaire (TFEQ-R21) and gastrojejunal anastomotic diameter were assessed. Nine and 34 patients underwent endoscopic suturing and sclerotherapy, respectively. The remainder underwent sclerotherapy. At 3 months, weight, ghrelin levels, eating behavior and outlet diameter were reassessed.

Results—Subjects were 47±10 years old, regained 43±26% of maximal lost weight. Ghrelin level was 123±106 ng/ml, outlet diameter 21±6.3 mm. At 3 months, the entire cohort lost 4.1±5.9% of total body weight (TBW) and showed improvement in cognitive eating habit ($p<0.01$).

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B. Abu Dayyeh: Data collection and analysis; drafting of the manuscript

C. Thompson: Study design, critical revision of the manuscript

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Endoscopic suturing and sclerotherapy patients lost 10.4 ± 2.2 %TBW and 2.7 ± 5.5 %TBW ($p < 0.01$). Suturing and sclerotherapy reduced the outlet diameter by 15.0 ± 6.7 mm and 2.6 ± 5.7 mm ($p < 0.01$). Ghrelin levels increased after suturing by 46 ± 55 ng/ml, decreased by 37 ± 110 ng/ml after sclerotherapy ($p = 0.02$). Suturing resulted in greater improvement in cognitive eating behavior than sclerotherapy ($p = 0.03$).

Reduction in outlet size and changes in cognitive and emotional eating behaviors were predictors of weight loss after GJAR on a univariate analysis. On a multivariate analysis, the only predictor of weight loss was a reduction in outlet size ($p < 0.01$).

Conclusions—Endoscopic suturing resulted in greater reduction in outlet size, improvement in eating behavior and weight loss than sclerotherapy. Reduction of anastomosis size was a significant predictor of weight loss after GJAR.

Keywords

Weight regain; TORe; sclerotherapy; endoscopic suturing; ghrelin

Introduction

Weight regain has been defined as an increase in BMI after an initial successful weight loss (defined as the percentage of excess weight loss (EWL) of equal to or greater than 50%) [1]. Nevertheless, there is no clear consensus on this definition (i.e. the amount of weight regain required). It is known that a gain of 5% to 10% of EWL results in recurrence of obesity-related comorbidities [2–4]. As many as 50% of bariatric patients may regain approximately 5% of their weight at 1 to 2 years following the surgery [5,6]. The weight regain continues and appears to level off at 8 to 10 years, with a 22% to 39% weight regain from maximal weight loss [6–8]. To date, the exact mechanisms of weight regain remain unknown. It has been hypothesized that a combination of genetic, anatomical, physiological and behavioral factors likely play a role. Recent studies have shown a positive correlation between a large gastrojejunal (GJ) anastomotic aperture and weight regain [9–11]. Thus, procedures that reduce the size of GJ anastomosis are appealing as a potential treatment for weight regain.

Traditionally, dilated GJ anastomosis has been treated with surgical revision. However, this approach is technically difficult and has a complication rate of over 15% and a mortality rate of up to 2% [12,13]. As a result, less invasive endoscopic techniques to reduce the anastomotic size have been developed over the past decade. This study will focus on two of the more commonly performed gastrojejunal anastomotic reduction (GJAR) techniques—endoscopic suturing for Transoral Outlet Reduction (TORe) and sclerotherapy.

Endoscopic suturing to reduce the GJ anastomotic aperture, also known TORe, for weight regain treatment was first described in 2004 [14]. Since then, many endoscopic suturing platforms have been developed and employed for this purpose. In the past, suturing devices relied on a suction-based mechanism to grab tissue [14]. However, a more modern suturing platform utilizes a curved suturing arm to deploy full-thickness sutures around the rim of the GJ anastomosis to reduce its diameter [15]. A randomized, blinded, sham-controlled trial has shown that patients who received endoscopic suturing procedures using the older suction-

based platform had significantly greater weight loss and improvement in co-morbidities than those who underwent a sham procedure. As a result, this study established level 1b evidence to support the use of endoscopic suturing to reduce GJ anastomotic size to treat weight regain [16]. Additionally, a recent matched cohort study comparing older suction-based suturing platforms to the newer device showed that the latter provided superior weight loss and durability [17].

In contrast, sclerotherapy involves injecting a sclerosant (usually sodium morrhuate) at various points around a dilated anastomosis to increase restriction, decrease compliance and reduce the size of the anastomosis. The procedure was first described by Spaulding in 2003 and resulted in an approximate weight loss of 4.5 kg at 6 month follow-up [18,19]. While both endoscopic suturing and sclerotherapy have been shown to be effective at treating weight regain, the exact mechanism by which they induce weight loss remains unclear. This study aimed to assess the effect of TORe and sclerotherapy on ghrelin levels (physiological effect), eating behavior (behavioral effect) and GJ anastomotic size (anatomical effect) in order to better understand the mechanisms of how they induced weight loss. Additionally, predictors of weight loss after endoscopic revision were also assessed.

Methods

Study Population

Forty-three consecutive RYGB patients who presented to our bariatric center of excellence for consultation of weight regain were enrolled. In this study, weight regain was defined as a gain of at least 20% of maximal weight lost after gastric bypass surgery. All patients were at least 1 year post surgery. At the initial visit, all patients underwent an intensive review of their supervised diet program and lifestyle modification regimen. If this was not adequate or could not be confirmed, the patients were referred back to our nutritionist for further care. All patients were then given details of the two anastomotic reduction procedures offered at our institution (TORe and sclerotherapy). Specifically, details on the techniques of the two procedures, possible adverse events, pre-procedural and post-procedural instructions, and expected estimate weight loss results based on previous literature were described. They were also informed that depending on their insurance coverage, only one of the procedures may be covered. The details of the study were then explained. All patients provided written informed consents. The study was performed at a tertiary referral center with bariatric center of excellence. Exclusion criteria included the presence of gastrogastic fistula, marginal ulceration, and use of weight loss medications.

Data Collection

Patient demographics, time duration from RYGB, weight and body mass index (BMI) were collected at the time of enrollment. Eating behavior was assessed at the time of enrollment and at 3 month follow-up using the 21-item Three-Factor Eating Questionnaire (TFEQ-R21), a validated self-assessment survey used to study eating behavior (Table 1) [20]. The questionnaire assessed 3 domains of eating behavior: cognitive restraint (CR), uncontrolled eating (UE), and emotional eating (EE). Patients were asked to respond to 21 questions on a four-point Likert scale for items 1-20 and on an eight-point numerical rating scale for item

21. Response to each item was given a score of 1 to 4. Items 1-16 were then reverse coded and item 21 was recorded as following: 1-2 as 1; 3-4 as 2; 5-6 as 3; 7-8 as 4. Domain scores were calculated using a mean of all items within each domain. Therefore, domain scores ranged from 1 to 4 with a higher score representing more cognitive restraint, uncontrolled and emotional eating behavior.

All subjects underwent a diagnostic upper endoscopy, where gastric pouch and GJ anastomotic sizes were measured. These parameters were again measured at 3 month follow-up endoscopy. The pouch length was measured using calibrated markings on the gastroscope (Olympus, Center Valley, PA, USA). The GJ anastomotic diameter was measured using a calibrated flexible measuring instrument (Olympus, Center Valley, PA, USA).

Fasting ghrelin levels were measured using a radioimmunoassay (RIA) kit (Linco Research, St. Charles, MO). Baseline ghrelin levels were measured prior to the anastomotic reduction procedures. For patients in the endoscopic suturing arm, the 3 month ghrelin levels were checked at a follow-up clinic visit. For patients in the sclerotherapy arm, the 3 month ghrelin levels were measured at either a follow-up clinic visit (if the patient did not undergo a repeat sclerotherapy session at 3 months) or prior to the next sclerotherapy session (if the patient was scheduled for a repeat sclerotherapy session at 3 months).

Procedures

Subsequently, patients underwent one of the two GJAR procedures. Specifically, nine out of 43 patients underwent endoscopic suturing for outlet reduction using the first generation of the Overstitch Endoscopic Suturing System (Apollo Endosurgery, Austin, TX). The remainder (n = 34) underwent sclerotherapy to reduce the GJ anastomotic size. The decision to perform one procedure over the other was based primarily on patients' anatomy and preference and their insurance coverage.

Details of both procedures were described in details in our prior work [15,19]. In brief, the Overstitch Endoscopic Suturing System attached to a double channel endoscope (GIF-2T160; Olympus America, Central Valley, Pennsylvania, USA). A curved suture arm extended from one channel, and an anchor exchange extended from the other. When the handle was closed, the tissue anchor and suture arm were advanced through the tissue, and the tissue anchor was passed from the suture arm into the anchor exchange. The handle was then opened and the tissue was released. The anchor could then be passed back to the suture arm for additional stitch patterns. In this study, interrupted suture pattern was used to place stitches from lower to upper margin and from right to left of the GJ anastomosis. The procedure was deemed technically successful when the GJ anastomotic diameter was reduced to less than 12 millimeters (mm).

Sclerotherapy was performed by injecting sodium morrhuate (Luipold Pharmaceuticals, Shirley, NY) into the rim of the GJ anastomosis using an endoscopic sclerotherapy needle. Two milliliter (ml) aliquots were injected circumferentially around the GJ anastomosis with a maximum dose of 30 ml.

Outcomes

Primary outcomes were fasting ghrelin levels (physiologic effect), eating behavior (behavioral effect) and GJ anastomotic diameter (anatomic effect) at 3 month follow-up. Secondary outcomes were follow-up weights at 3 and 9 months post procedure.

Statistical Analysis

Pearson correlation and Student's *t*-test were used to compare continuous, normally distributed variables. Multivariate linear regression was used to determine the predictors of weight loss after GJAR procedures. Standardized β coefficients were reported and a significant two-sided *p*-value was set at 0.05. All statistical modeling was performed using SAS version 9.2 software (Cary, NC, USA). The protocol was approved by the Institution Review Board (IRB) committee.

Results

Clinical Characteristics

Clinical characteristics of the 43 patients are summarized in Table 2. On average, patients were 47 ± 10 years old and were 6 ± 5 years post gastric bypass. At the time of GJAR, they had regained $43 \pm 26\%$ of maximal weight lost. Baseline ghrelin levels were 123 ± 106 ng/ml. Average TFEQ-R21 scores for cognitive restraint, uncontrolled eating and emotional eating behavior were 2.3, 2.6 and 2.6, respectively. Average outlet size prior to GJAR was 21 ± 6.3 mm. Patient characteristics were similar between the endoscopic suturing and the sclerotherapy arms (Table 2).

Effects of Gastrojejunal Anastomotic Reduction on Weight, Ghrelin Levels, Eating Behavior and GJ Anastomotic Aperture

All 43 patients underwent GJAR successfully. Nine out of 43 patients underwent endoscopic suturing, and the remaining 34 patients underwent sclerotherapy. All patients were discharged from the endoscopy unit on the day of the procedure. Peri-procedural adverse events included abdominal pain (2 in the suturing arm, 1 in the sclerotherapy arm), heartburn (1 in the sclerotherapy arm), hypertensive urgency (1 in the sclerotherapy arm) that spontaneously resolved, and bleeding (1 in the sclerotherapy arm) that was treated successfully with epinephrine injection and clipping.

At 3 months, 38 out of 43 patients presented for follow up (88% follow up rate). Out of the 38 patients, seven underwent endoscopic suturing (78% follow up rate) and 31 underwent sclerotherapy (91% follow up rate). On average, patients for the entire cohort lost 5.0 ± 6.8 kg representing $4.1 \pm 5.9\%$ total body weight loss (TBWL) ($p=0.0002$). Average BMI decreased from 40.2 ± 7.5 kg/m² at baseline to 37.9 ± 5.2 kg/m² at 3 months.) There were no significant changes in ghrelin levels for the entire cohort. Specifically, plasma ghrelin levels decreased by 7 ± 8.7 ng/ml, but this change was not significant ($p=0.58$). An improvement in the cognitive restraint domain of the TFEQ-R21 eating behavior ($p<0.01$) was observed. Uncontrolled eating and emotional eating habits remained the same ($p=0.07$ and 0.22 , respectively). Stoma size decreased by 5.0 ± 7.5 mm ($p<0.0003$) (Table 3).

Overall, patients who underwent endoscopic suturing lost a greater amount of weight, showed more improvement in eating behavior (cognitive restraint domain), and had a smaller anastomotic size at 3 month follow-up compared to those who underwent sclerotherapy (Table 3). Fasting ghrelin levels increased after endoscopic suturing by 46+55 ng/ml, but decreased by 37+110 ng/ml after sclerotherapy ($p=0.02$).

At 9 months, follow up weights were available for 30 out of 43 patients (70% follow up rate). These included six patients from the endoscopic suturing arm (67% follow up rate) and 22 patients from the sclerotherapy arm (71% follow up rate). Overall, the patients lost 7.8 ± 11.2 kg, which represented $7.4\pm 8.4\%$ TBWL ($p=0.0001$). Average BMI decreased from 40.2 ± 7.5 kg/m² at baseline to 36.4 ± 5.0 kg/m² at 9 months (Table 3). On average, each patient in the sclerotherapy arm received a median of 2 sessions of sclerotherapy (range 1-3) during the 9 month period. Only 25% of these patients received 1 sclerotherapy session.

Predictors of Weight Loss

On a univariate linear regression, the cognitive restraint domain of eating behavior, the emotional eating domain of eating behavior and the GJ anastomotic size were correlated with the amount of weight loss after GJAR. However, on a multivariate linear regression, only the degree of GJ anastomotic size reduction remained significantly correlated with the amount of weight loss after GJAR (Table 4).

Discussion

This study demonstrated that gastrojejunal anastomotic reduction procedures resulted in weight loss, a smaller anastomotic aperture and improvement in the cognitive restraint domain of eating behavior at 3 months. Additionally, ghrelin levels increased after endoscopic suturing, but decreased after sclerotherapy at 3 months. On a univariate linear regression, predictors of weight loss after anastomotic reduction procedures included a decrease in the GJ anastomotic size, the changes in cognitive restraint and emotional eating domains of eating behavior. However, on a multivariate regression model, only reduced GJ anastomotic size remained a significant predictor of weight loss. This suggested that the changes in eating behavior were likely collinear with and attributed to outlet reduction.

In this study, there were no significant changes in plasma ghrelin levels at 3 months after GJAR when patients who underwent endoscopic suturing and sclerotherapy were analyzed together. However, the subgroup analysis demonstrated that patients who underwent endoscopic suturing had an increase in ghrelin levels at 3 months. In contrast, patients who underwent sclerotherapy experienced a decrease in ghrelin levels after the procedure.

Ghrelin is a neuropeptide that is produced primarily by the A/X cells in the gastric fundus [22]. It functions as a “hunger hormone” by inducing hunger, gastric acid secretion and gastrointestinal motility to prepare the body in anticipation of a meal [23]. Prior studies have demonstrated that ghrelin levels increase after gastric banding surgery, but decrease after sleeve gastrectomy and RYGB [24–29]. The difference in these findings is likely due to variation of surgical techniques. Gastric banding involves placing an inflatable band around the proximal stomach. The fundus is reserved and still a part of a new smaller stomach

pouch. In contrast, sleeve gastrectomy and RYGB involve complete separation of the fundus, which is the prominent area of ghrelin secretion.

In some way, endoscopic suturing for outlet reduction may be viewed as being similar to gastric banding. Specifically, they are both restrictive in nature. Ghrelin-producing cells remain intact in both procedures. The observed increase in ghrelin levels after endoscopic suturing is therefore likely a result of weight loss from the procedure (the body's response to maintain stable body weight). In comparison, sclerotherapy involves injecting a sclerosant around the rim of a dilated GJ stoma. This technique likely leads to necrosis of cells around the stoma, some of which may include ghrelin-producing cells. This therefore leads to a decrease in ghrelin levels as observed in our study.

Despite an increase in ghrelin levels, patients who underwent endoscopic suturing for outlet reduction experienced a greater amount of weight loss than those who underwent sclerotherapy. This was likely explained by a greater reduction in the stoma size seen at 3 month follow-up endoscopy in the suturing arm (15 mm reduction in diameter) compared to the sclerotherapy arm (2.6 mm reduction in diameter). This result therefore further strengthened our finding that the reduction in GJ stoma size was a significant predictor of successful weight loss after GJAR procedures, and not ghrelin levels.

The strengths of this study included its prospective design and the inclusion of anatomical, physiological and behavioral parameters into the analysis. Stoma sizes were measured in a uniform fashion to minimize variability. The research team (who handled the ghrelin analysis and who administered the TFEQ-R21 questionnaire) and the endoscopy team (who handled the stoma size measurement) were blinded to patients' weight profile. Limitations of this study included a relatively small sample size. However, despite the size, our study was able to detect significant changes in weight, anastomotic size, ghrelin levels and the cognitive restraint domain of the eating behavior between the suturing and the sclerotherapy arms. In this study, patients were not randomized primarily due to patients' preference and anatomy, procedural cost and insurance coverage. Additionally, the definition of weight regain is not universal as there currently is no universally accepted quantitative definition for weight regain [2,3]. Nevertheless, patients often report weight regain and recurrence of comorbid illnesses and request therapy. At our institution, patients are not eligible for endoscopic intervention unless they have regained at least 20% of maximal weight lost after gastric bypass. Additionally, while clinical outcome (follow-up weight) was available at 3 and 9 months, primary outcome data (the anatomical, physiological and behavioral effects of TORe) were available only at 3 months. A prospective study with a longer follow-up period may be useful, although it is possible that the effect of GJAR is maximized at around 3 months after the procedure. Lastly, a prospective study comparing the anatomic, behavioral and physiologic effects of these procedures to a sham procedure may be further considered.

In conclusion, this study suggests that the mechanisms for the weight loss effect of endoscopic suturing TORe and sclerotherapy likely involve a reduction in the stoma size (anatomic effect) and an improvement in the cognitive restraint domain of eating behavior (behavioral effect). Ghrelin levels (physiologic effect) vary based on the type of endoscopic revision. Additionally, this study suggests that endoscopic suturing TORe appears to be

more effective than sclerotherapy at treating weight regain likely due to its greater effect on gastrojejunal anastomotic size reduction.

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Figure 1. Changes in TFEQ-R21 domains after endoscopic reduction of the GJ stoma diameter

Table 1
TFEQ-R21 Questionnaire

Cognitive Restraint (CR)	
1	I deliberately take small helpings to control my weight Definitely true/mostly true/mostly false/definitely false
2	I start to eat when I feel anxious Definitely true/mostly true/mostly false/definitely false
3	Sometimes when I start eating, I just can't seem to stop Definitely true/mostly true/mostly false/definitely false
4	When I feel sad, I eat too much Definitely true/mostly true/mostly false/definitely false
5	I don't eat some foods because they make me fat Definitely true/mostly true/mostly false/definitely false
6	Being with someone who is eating, often makes me want to also eat <i>Definitely true/mostly true/mostly false/definitely false</i>
Uncontrolled Eating (UE)	
	7. When I feel tense or "wound up," I often feel I need to eat Definitely true/mostly true/mostly false/definitely false
	8. I often get so hungry that my stomach feels like a bottomless pit Definitely true/mostly true/mostly false/definitely false
	9. I'm always so hungry that it's hard for me to stop eating before finishing all of the food on my plate Definitely true/mostly true/mostly false/definitely false
	10. When I feel lonely, I console myself by eating Definitely true/mostly true/mostly false/definitely false
	11. I consciously hold back on how much I eat at meals to keep from gaining weight Definitely true/mostly true/mostly false/definitely false
	12. When I smell a sizzling steak or see a juicy piece of meat, I find it very difficult to keep from eating—even if I've just finished a meal Definitely true/mostly true/mostly false/definitely false
	13. I'm always hungry enough to eat at any time Definitely true/mostly true/mostly false/definitely false
	14. If I feel nervous, I try to calm down by eating Definitely true/mostly true/mostly false/definitely false
	15. When I see something that looks delicious, I often get so hungry that I have to eat right away Definitely true/mostly true/mostly false/definitely false
Emotional Eating (EE)	
	16. When I feel depressed, I want to eat Definitely true/mostly true/mostly false/definitely false
	17. How often do you avoid "stocking up" on tempting foods? Almost never/seldom/usually/almost always

18. How likely are you to make an effort to eat less than you want?

Unlikely/a little likely/somewhat likely/very likely

19. Do you go on eating binges even though you're not hungry?

Never/rarely/sometimes/at least once a week

20. How often do you feel hungry?

Only at meal times/sometimes between meals/often between meals/almost always

21. On a scale from 1 to 8, where 1 means no restraint in eating and 8 means total restraint, what number would you give yourself?

1 2 3 4 5 6 7 8

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Table 2
Patient characteristics

	All (n = 43)	Endoscopic Suturing (n = 9)	Sclerotherapy (n = 34)	p-value
Age (years) (mean, SD)	47 (10)	47 (13)	47 (9)	1.00
Gender (% female)	91	89	91	1.00
Weight regain from nadir (%) (mean, SD)	43 (26)	58 (35)	40 (24)	0.17
Years from RYGB (mean, SD)	6 (5)	7 (4)	6 (5)	0.90
Ghrelin level (ng/ml) (mean, SD)	123 (106)	89 (35)	132 (117)	0.07
TFEQ-R21 (mean, SD)				
•Cognitive restraint	2.3 (0.4)	2.2 (0.2)	2.4 (0.4)	0.11
•Uncontrolled eating	2.6 (0.6)	2.9 (0.6)	2.5 (0.6)	0.20
•Emotional eating	2.6 (0.8)	2.5 (1.1)	2.6 (0.7)	0.91
Gastrojejunal stoma diameter (mm) (mean, SD)	21 (6.3)	23 (6)	21 (6)	0.33

Changes in weight, ghrelin levels, eating behavior and gastrojejun anastomotic size after endoscopic suturing and sclerotherapy

Table 3

	All (n = 43)	p-value ⁱⁱⁱ	Endoscopic Suturing (n = 9)	Sclerotherapy (n = 34)	p-value
Primary Outcomes					
Change in ghrelin level (ng/ml) (mean, SD)	-7 ± 8.7	0.58	46 ± 55	-37 ± 100	0.02
Change in TFEQ-R21 scores					
•Cognitive restraint	0.2 ± 0.3	<0.01	0.4 ± 0.5	0.1 ± 0.3	0.03
•Uncontrolled eating	-0.1 ± 0.4	0.07	-0.1 ± 0.4	-0.1 ± 0.4	>0.05
•Emotional eating	-0.2 ± 0.6	0.22	-0.4 ± 0.4	-0.1 ± 0.6	0.17
Change in stoma diameter (mm) (mean, SD)	-5.0 ± 7.5	0.0003	-15 ± 6.7	-2.6 ± 5.7	<0.01
Secondary Outcomes					
Weight loss at 3 months ⁱ (%TBWL) (mean, SD)	4.1 ± 5.9*	0.0002	10.4 ± 2.2	2.7 ± 5.5	<0.01
Weight loss at 9 months ⁱⁱ (%TBWL) (mean, SD)	7.4 ± 8.4*	0.0001	12.3 ± 12.6	6.1 ± 6.8	0.29

ⁱ weight data available for 38 patients

ⁱⁱ weight data available for 30 patients.

ⁱⁱⁱ p-value of the comparison to the baseline levels prior to gastrojejun anastomotic reduction procedures.

Table 4
Predictors of weight loss after endoscopic reduction of GJ stoma diameter

	Univariate Standardized β coefficient	P value	Multivariate Standardized β coefficient	P value
Change in ghrelin levels (ng/ml)	-0.1	0.55	0.03	0.98
Change in TFEQ-R21				
•Cognitive restraint	-0.34	0.03	-0.11	0.44
•Uncontrolled eating	0.23	0.116	0.02	0.88
•Emotional eating	0.43	0.006	0.27	0.052
Decrease in GJ anastomotic size (mm)	0.64	<0.01	0.51	<0.01