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Changes in Gastrointestinal Hormones and Leptin After Roux-en-Y Gastric Bypass Surgery

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Abstract

Background—Roux-en-Y gastric bypass (RYGB) imparts long-term weight loss, the mechanisms for which are not well understood. Changes in leptin and gastrointestinal (GI) hormones, including glucagon-like peptide 1 (GLP-1), peptide YY (PYY), and ghrelin, may contribute to the relative success of RYGB compared with conventional weight loss methods. This study evaluated changes in GI hormones and leptin post-RYGB. The study also evaluated whether GI hormones differed after a short-term dose of protein or fat.

Methods—GLP-1, PYY, ghrelin, and leptin were assessed in 16 women before RYGB and up to 1 year after RYGB. Plasma was collected before and at several times after a short-term equicaloric dose of protein or fat.

Results—GLP-1 area under the curve (AUC) increased at week 6 and 1 year in the fat beverage (FAT-BEV) group compared with baseline. PYY AUC remained elevated at 1 year in the FAT-BEV group. Ghrelin AUC decreased at week 2, week 6, and 1 year in the protein beverage (PRO-BEV) group compared with baseline. Ghrelin AUC was lower in the PRO-BEV group compared with the FAT-BEV group at week 6. Fasted leptin decreased at all visits in both groups and was lower in the FAT-BEV group compared with the PRO-BEV group at 1 year.

Conclusions—Changes from baseline were evident for all GI hormones and leptin; some differences were evident soon after surgery (ghrelin, leptin), whereas others were maintained long term (GLP-1, PYY, ghrelin, leptin). In response to a short-term stimulus, protein suppressed ghrelin and fat potentially stimulated GLP-1 and PYY. Future work in this area is warranted.

Keywords

obesity; ghrelin; peptide YY; glucagon-like peptide 1; leptin; gastric bypass; gastrointestinal hormones

Introduction

Bariatric surgery is the most effective treatment for morbid obesity in terms of achieving major, long-term weight loss.⁰¹ Consequently, the prevalence of such surgery is increasing worldwide. Roux-en-Y gastric bypass (RYGB) is the most common bariatric procedure performed, comprising about 70% to 75% of all bariatric procedures.² The RYGB procedure imparts substantial long-term weight loss; however, the mechanisms by which this occurs are not well understood. Restriction and bypass components characterize this procedure.³ The restrictive component is achieved by creating a gastric pouch (~20–30 mL), which promotes early satiety^{4,5} and thereby decreases dietary intake,⁵ which is considered to be the primary reason for weight loss after RYGB.⁶ In addition, the distal stomach, duodenum, and proximal jejunum are bypassed.⁴ Malabsorption of energy-yielding macronutrients is not common after RYGB, but in some cases malabsorption of micronutrients (eg, iron, vitamin B₁₂) does occur.^{7,8} In addition to these physiological modifications, changes in leptin and several gastrointestinal (GI) hormones, including glucagon-like peptide 1 (GLP-1), peptide YY (PYY), and ghrelin, may explain the relative success of the RYGB procedure.^{9,10}

GLP-1 and PYY are considered appetite-regulating hormones, given that secretion of each reduces hunger and imparts satiety.¹¹ They are secreted from the L cells of the distal ileum and colon in response to enteral nutrient intake.^{12–18} The mechanism by which these hormones promote satiety is thought to be multifaceted because they slow gastric emptying,^{16,19,20} promote insulin release,^{16,21} and inhibit gastric acid secretion.^{19,20} Because of these effects, they are considered to play an important role in the “ileal brake” mechanism,²² which regulates the passage of nutrients through the GI tract.²³ GLP-1 and PYY are secreted within 15 to 30 minutes after food intake.^{24–26} More specifically, data suggest that GLP-1 is stimulated by fat intake in rats²⁷ and humans,^{28,29} and other data support that it is stimulated by protein intake more than carbohydrate intake.^{30,31} Similarly, fat^{32–34} and protein^{32,35,36} have been found to be important regulators of PYY secretion in obese^{32,35,36} and normal-weight individuals.^{33,34,36} Some data support that fasting and postprandial GLP-1 and PYY secretion are higher in normal-weight individuals compared with those who are obese or overweight.^{37–40} Higher GLP-1 and PYY levels have been reported in post-RYGB patients compared with pre-RYGB,^{9,11,41–44} normal-weight,^{11,44–47} over-weight,^{46,48,48–50} and obese individuals^{11,44,45,51} and those who undergo other weight loss surgeries.^{11,46,48,48,50}

Ghrelin is the only GI hormone known to stimulate appetite, and therefore, it is considered to be orexi-genic.^{13–15,17} It is released both centrally (hypothalamus) and peripherally (stomach), and its antisatiating properties may be due to its biological effects to increase GI motility and decrease insulin secretion.^{13,52} Ghrelin levels increase in the absence of enteral intake and decrease right after meal initiation,⁵³ and the macronutrient that induces the

greatest suppression is not well defined. For instance, some research suggests that carbohydrates are suppressive,^{54,55} whereas others have found protein to be more potent in terms of prolonged suppression.^{30,31,55–58} Erdmann et al⁵⁴ also found that fat was a potent suppressor, especially in the late postprandial state (ie, 60–180 minutes), with similar findings by Tannous dit El Khoury et al.⁵⁵ In addition, increased ghrelin levels have been reported in individuals undergoing diet-induced weight loss, which might explain the difficulty in maintaining weight loss achieved with conventional methods.⁵⁹ However, reduced ghrelin has been reported after RYGB weight loss compared with pre-RYGB,^{60–63} normal-weight,^{11,45,59,61,63–65} overweight,^{46,48} and obese^{45,59,61,65,66} people and/or those who undergo other restrictive bariatric surgical procedures.^{46,48,65} However, not all research has found this to be the case^{7,9,41,44,66–73}; therefore, the role of ghrelin in post-RYGB weight loss remains unclear.

The adipocytokine leptin is a product of the obesity gene (ob gene) and is understood to be involved in long-term energy balance.⁷⁴ It is secreted mainly by adipocytes and, to a lesser degree, gastric chief cells⁷⁵ and influences energy intake, primarily by acting on the hypothalamus^{17,74,76} to decrease food intake and increase energy expenditure.⁷⁶ Plasma leptin concentrations are not known to be regulated by macronutrients but rather are regulated by adipose tissue mass. Leptin circulates in proportion to whole-body adipose tissue mass,⁷⁴ and strong evidence exists that leptin decreases with a reduction in adipose tissue.^{77–80} As would be expected, decreased leptin has been reported in post-RYGB patients compared with pre-RYGB,^{9,63,73,78,81–91} normal-weight,⁹² overweight,⁴⁶ and obese^{49,70,93} patients.

The objective of this study was to evaluate the changes in GLP-1, PYY, ghrelin, and leptin concentrations post-RYGB. In addition, we sought to determine whether there was a difference in GI hormone levels after a short-term dose of either protein or fat.

Methods

Women with class III obesity (ie, body mass index [BMI] ≥ 40 kg/m²) who planned to undergo the laparoscopic RYGB procedure were recruited from the Weight Loss Surgery Center at the University of Minnesota Medical Center–Fairview. Participants for this longitudinal analysis were also enrolled in a broader longitudinal study investigating body composition and metabolic changes after RYGB surgery. This study included 5 visits that were 24 hours in duration: 30 to 70 days before RYGB (baseline); 2 weeks post-RYGB (week 2); 6 weeks post-RYGB (week 6); 6 months post-RYGB (month 6); and 1 year post-RYGB (1 year). The timing of the study visits was established in order to evaluate the clinical outcomes in both the early (ie, weeks 2 and 6) and late (ie, month 6 and 1 year) postoperative stages. GI hormones and leptin were analyzed in 16 participants. Exclusion criteria included the following: use of corticosteroids, testosterone, or anabolic agents; internally placed biomedical device (eg, pacemaker); liver, renal, or heart failure; pulmonary hypertension; thyroid disease (included if treated and within normal limits); neoplastic disease; type 1 or uncontrolled type 2 diabetes mellitus (defined by hemoglobin A_{1c} >7%); pregnancy; or previous weight loss surgery. The study protocol was reviewed and approved by the Institutional Review Board and the General Clinical Research Center (GCRC) at the

University of Minnesota, and participants provided written informed consent before enrollment in the study.

The day before admission to the GCRC, participants were instructed to avoid caffeine, alcohol, and vigorous exercise for 24 hours before testing. Participants were also asked to be in the fasted state for at least 2 hours before GCRC admission. Participants were randomized to 1 of 2 groups: (1) PRO-BEV group: those receiving a sugar-free, high-protein beverage (20 g protein, 0 g fat, 2 g carbohydrate, 90 kcal, 8 oz) (protein: whey protein isolate, supplied by Davisco Foods International, Eden Prairie, MN), and (2) FAT-BEV group: those receiving a sugar-free, high-fat beverage (0 g protein, 9 g fat, 3 g carbohydrate, 90 kcal, 8 oz). At all visits, a baseline 4-hour fasted plasma sample was collected for the GI hormone and leptin analyses, and 15 minutes later, participants consumed the assigned beverage over a period of not more or less than 30 minutes (60 minutes at week 2 to accommodate the reduced stomach capacity). Blood draws were taken at specific time points after initiation of beverage consumption (time 0). All plasma samples were stored at -70°C before analysis of GLP-1, PYY, ghrelin, and leptin concentrations. Tables 1 and 2 depict when the hormones were sampled at each visit.

The longitudinal study from which these data were analyzed was originally aimed to investigate clinical outcomes, including body composition, energy metabolism, and changes in nutrition status after RYGB. One of the components of the longitudinal study was a double-blinded, randomized, 6-week supplementation period immediately after surgery to determine whether patients consuming more protein in the early postoperative period would lose less lean tissue. The participants consumed the randomly assigned beverage at each testing visit as described above and were also instructed to consume 2 of the assigned beverages daily throughout the initial 6-week postoperative period. For the purposes of this analysis, only the short-term response data from the beverage consumed at the testing visits are discussed.

Dietary Intake Assessment

Information regarding dietary intake was obtained through the use of diet records. During the week before each testing visit, participants recorded their food intake on 2 assigned weekdays and 1 weekend day. During the 6-week supplementation period (visits at weeks 2 and 6), participants were instructed to record study beverage intake. Recording errors were minimized by providing the participants with detailed instructions on how to record their intake, including estimation of portion size. Diet records were reviewed with the participants at each testing visit and were analyzed later for nutrient content using the Food Processor SQL software (version 10.4; ESHA Research, Salem, OR). To obtain an estimate of the participants' intake during the week before the visit, an average of the recorded macronutrients and calories was calculated.

Gastrointestinal Hormone and Leptin Assays

All samples were assayed in duplicate. PYY-like immunoreactivity was measured with a specific and sensitive radioimmunoassay that measured both the full length (PYY₁₋₃₆) and the fragment (PYY₃₋₃₆).^{38,94} Plasma active GLP-1 and total ghrelin were measured by

established in-house radioimmunoassay.^{95–97} Plasma leptin was measured with a Linco Research (Weldon Spring, MO) assay kit.

Anthropometric Measurements

Height and weight were measured using standardized procedures. Height was measured to the nearest 0.1 cm by a wall-mounted stadiometer (model S100; Ayrton Corporation, Prior Lake, MN) at baseline only. At all testing visits, weight was measured to the nearest 0.1 kg on a digital scale (model 5002; Scale-Tronix, White Plains, NY). BMI was calculated as the patient's weight in kilograms divided by her height in meters squared (kg/m^2).

Surgical Technique

All RYGB procedures were performed laparoscopically. A small gastric pouch (approximately 15 mL) was created, and the duodenum and proximal portion of the jejunum were bypassed to create a Roux limb. In most cases, the length of the Roux limb was 150 cm, according to Weight Loss Surgery Center at the University of Minnesota Medical Center–Fairview protocol.

Statistical Analysis

Study end points were defined as change from the baseline visit in body weight, fasted GI hormone levels, and fasted leptin and change from baseline in area under the curve (AUC) for GLP-1, PYY, and ghrelin. AUC for the week 2 visit was rescaled to the same length of time as the other visits for comparability. Supplement groups were compared in mixed-effects linear models with a random effect to model the correlation of repeated measurements within each participant. SAS 9.2 software (SAS Institute, Cary, NC) was used for statistical analyses.

Results

Twenty-nine women participated in the study. GI hormone and leptin levels were analyzed in only the 16 women who completed all 5 study visits and who had a sufficient amount of plasma for analyses. All participants were Caucasian, with a mean $\pm$ standard deviation age of 49 ± 9 years. At baseline, there were no statistically significant differences between the groups in terms of age, weight, height, or BMI (Table 3). In both groups, BMI and absolute body weight decreased significantly at month 6 and 1 year compared with baseline. At month 6, weight decreased by a mean 34 kg (27% weight loss), and at 1 year, weight decreased by a mean 43 kg (34% weight loss).

Body Weight Change From Baseline Visit

Change in body weight for all 29 participants is reported in Figure 1. Weight loss was significant at all visits in both treatment groups, with no differences between treatment groups.

Dietary Intake Assessment

At the baseline visit, the FAT-BEV group was consuming significantly more calories than the PRO-BEV group ($2,305 \pm 456$ kcal vs $1,696 \pm 457$ kcal, respectively; $P = .02$). For the

remainder of the study, no differences in caloric intake were evident between the 2 treatment groups. At week 2, participants reported consuming on average 385 kcal (range, 101–963 kcal) per day. By week 6, caloric levels increased to an average 692 kcal (range, 397–1,150 kcal) per day. At week 26, participants were consuming about 1,120 kcal (range, 645–1,565 kcal) a day, and by the 1-year follow-up visit, participants reported consuming about 1,350 kcal (range, 755–1,774 kcal) per day.

At the baseline visit, the FAT-BEV group was consuming significantly more protein than the PRO-BEV group (76 ± 26 g vs 105 ± 27 g, respectively; $P < .05$). However, by week 2, the PRO-BEV group was consuming significantly more protein than the FAT-BEV group (41 ± 24 g vs 11 ± 15 g; $P = .01$, respectively), and this difference remained significant at week 6 (PRO-BEV 57 ± 9 g vs FAT-BEV 36 ± 25 g, $P = .04$). This discrepancy in protein intake between the 2 groups at weeks 2 and 6 is due to the fact that we asked the participants in both groups to consume the assigned beverage for 6 weeks (ie, immediately after surgery until the week 6 visit). Participants were instructed to drink the assigned beverage twice a day in addition to consuming their regular meals and snacks. Therefore, the PRO-BEV group was potentially receiving an additional 40 g of protein per day. Protein consumption was no longer different between the groups at month 6 (59 g/d) and 1 year (65 g/d).

There were no differences in fat consumption between the groups at any visit. At baseline, participants reported consuming an average 82 g of fat per day. At week 2, fat consumption decreased and was about 12 g/d. At week 6, fat consumption increased, and participants reported an average intake of 25 g/d. Fat consumption continued to increase, and average reported intakes were 44 g at month 6 and 53 g at 1 year.

GLP-1 AUC Change From Baseline Visit

In the FAT-BEV group, GLP-1 AUC significantly increased at week 6 and 1 year post-RYGB compared with baseline (Figure 2).

PYY AUC Change From Baseline Visit

In both the PRO-BEV and FAT-BEV groups, PYY AUC significantly increased at month 6 compared with baseline (Figure 3). In addition, PYY AUC remained higher compared with baseline at 1 year post-RYGB in the FAT-BEV group.

Ghrelin AUC Change From Baseline Visit

Ghrelin AUC was significantly lower at week 2 compared with baseline in the PRO-BEV group (Figure 4). Moreover, this alteration remained significant at week 6 and 1 year. Ghrelin AUC levels were significantly different between the PRO-BEV and FAT-BEV group at week 6, with lower levels in the PRO-BEV group.

Fasted GLP-1 Change From Baseline Visit

At month 6, fasted GLP-1 increased significantly compared with baseline in the FAT-BEV group (Figure 5). No differences in fasted GLP-1 levels between treatments were evident at any visit.

Fasted PYY Change From Baseline Visit

No significant differences in fasted PYY levels were evident between visits (data not presented). There was no difference in fasted PYY levels between treatment groups at any visit.

Fasted Ghrelin Change From Baseline Visit

Fasted ghrelin was significantly lower at week 2, week 6, and 1 year post-RYGB compared with the baseline visit in the PRO-BEV group (Figure 6). At week 2, fasted ghrelin was significantly different between treatments, with lower levels in the PRO-BEV group.

Fasted Leptin Change From Baseline Visit

In both the PRO-BEV and FAT-BEV groups, leptin significantly decreased compared with baseline at all time points after RYGB (Figure 7). Leptin levels were significantly different between the PRO-BEV and FAT-BEV groups at 1 year, with lower leptin in the FAT-BEV group.

Discussion

This study investigated the effect of the RYGB procedure on body weight and levels of GLP-1, PYY, ghrelin, and leptin. We also evaluated the effect of short-term administration of protein and fat on GI hormone levels. In patients with morbid obesity, RYGB resulted in significant weight loss, which was maintained for at least 1 year after surgery. In addition to the favorable change in weight, alterations in GI hormones and leptin also occurred, and in some cases these changes were macronutrient specific.

General Findings for Both Beverage Groups

Similarities between treatment groups were evident for fasted leptin at all visits and PYY AUC at month 6. In regard to fasted leptin, the adipocytokine decreased from baseline at all visits. This was an expected result and similar to what has been previously reported. Decreased leptin has consistently been found after a reduction in adipose tissue mass after weight loss, either by conventional methods^{78–80} or via RYGB.^{9,46,49,63,70,73,78,81–93} Of interest, however, we observed that fasted leptin was significantly different as soon as 2 weeks post-RYGB, before significant changes in absolute body weight were observed. This immediate change was also found by Rubino et al⁸⁵ at 3 weeks post-RYGB, before significant weight changes and might be a result of the RYGB procedure itself. Leptin is secreted in proportion to adipose tissue mass,⁷⁴ and it would be expected that this change would not occur until a later follow-up visit (eg, month 6). In addition to adipocytes, leptin is secreted from the stomach,⁷⁵ which is substantially altered after RYGB. This manipulation might explain the decreased fasted leptin levels we found soon after surgery.

PYY AUC was higher in both groups at 6 months post-RYGB compared with baseline. Our results are similar to those who have evaluated PYY level at 6 months post-RYGB.^{7,9} However, we are not aware of any study that has looked at the effect of different macronutrients on PYY level in the post-RYGB state. Given what has been reported in

overweight and normal-weight individuals, we expected PYY to increase after a short-term dose of either protein^{32,35,36} or fat,^{32–34} which is in line with our results.

Specific Findings—Protein Beverage Group

In the PRO-BEV group, a short-term dose significantly lowered ghrelin AUC at 2 weeks, 6 weeks, and 1 year post-RYGB compared with baseline levels. In terms of the ghrelin AUC results at 2 weeks, this early change is congruent with what has been found in previous research 30 minutes to 10 days after surgery^{60,62} and, similar to leptin, occurred before a significant change in absolute body weight occurred, suggesting that a component of the RYGB procedure is involved in this result. Through repeated measurements before, during, and after the RYGB procedure, Lin et al⁶² found that the greatest decline in ghrelin occurs after complete division of the stomach, offering an explanation as to why this favorable change was observed so soon after surgery. In terms of the macronutrient effect on ghrelin AUC, the fact that we found an effect in the PRO-BEV group after RYGB is a novel result. To our knowledge, no study has compared the effect of macronutrients on ghrelin in the post-RYGB state. We expected that protein would suppress ghrelin AUC in our patient population at 2 weeks post-RYGB, because research done in overweight and obese individuals indicates that ghrelin is lower after protein intake compared with the respective baseline levels,^{55,57} carbohydrate intake,^{30,31,55,56} and/or fat intake.⁵⁵ However, more research is needed in this area to clarify whether the ghrelin response post-RYGB is macronutrient specific. Such research has the potential to better define the diet recommendations for patients post-RYGB.

Ghrelin AUC was also significantly reduced at 6 weeks post-RYGB compared with both baseline and the FAT-BEV group. By this time point, participants had a significant change in body weight yet were still considered to be obese. Limited research has evaluated ghrelin at 6 weeks post-RYGB, and contrary findings are evident. At 4 weeks post-RYGB, Sundbom et al⁶⁹ reported an increase in ghrelin to levels comparable with pre-RYGB, whereas 2 studies^{63,78} did not find a significant ghrelin suppression compared with pre-RYGB levels. In addition, le Roux et al⁴¹ found an insignificant increase in ghrelin at 6 weeks compared with baseline. Discrepancies might be related to differences in study protocol. For example, Morínigo et al⁶³ measured ghrelin after a mixed 398-kcal liquid meal with 14.5% protein, and le Roux et al⁴¹ measured ghrelin after a mixed 400-kcal meal (protein amount not specified), whereas Sundbom et al⁶⁹ measured only fasted ghrelin. Olivan et al⁷⁸ measured ghrelin after a 50-g oral glucose tolerance test. We measured ghrelin after a 90-kcal protein beverage (88.9% protein), and our significant finding might be due to the higher proportion of protein. Studies that evaluated patients of similar weight status (obese and/or overweight) have observed protein to potentially suppress ghrelin.^{30,31,56,57} Although fat has been found to suppress ghrelin,^{54,55} we did not find this at week 6 and instead observed significantly lower ghrelin in the PRO-BEV group compared with the FAT-BEV group. Perhaps the best explanation is that protein may be more suppressive of the GI hormone than fat,^{55,57} especially in post-RYGB patients. Satiety research suggests that protein is the most satiating, and fat the least satiating,⁹⁸ which may account for our findings.

The suppressed ghrelin AUC levels observed at week 2 and 6 were maintained long-term in this study. Ghrelin AUC was significantly suppressed at 1 year post-RYGB compared with baseline levels. At this time point, almost half of the participants were considered to be overweight ($n = 7$) with the remainder still classified as obese ($n = 9$). Reduced ghrelin levels have been reported in RYGB patients 1 to 2 years postsurgery, compared with other surgical procedure patients⁶⁵ and obese^{45,65} and normal-weight individuals.^{45,65} This finding of suppressed ghrelin levels at 1 year post-RYGB is encouraging and might offer a long-term explanation for the relative success of the procedure. Future work should compare weight loss outcomes with ghrelin levels to better establish ghrelin's role in weight loss after RYGB.

Fasted ghrelin was significantly lower at weeks 2 and 6 and 1 year compared with baseline in only the PRO-BEV group and was significantly lower than in the FAT-BEV group at week 2. Treatment-specific alterations in the fasted ghrelin levels were unexpected and prompted us to investigate our diet data for possible explanations. As described in the Methods, this analysis was part of a larger study evaluating body composition changes and the impact of protein intake on those changes in the RYGB patient population and was not initially designed to evaluate GI hormones and leptin. Consequently, participants in this study only fasted for 4 hours before the baseline blood draw. At weeks 2 and 6, analysis of the meal eaten 4 to 6 hours before the baseline blood draw indicated that the percentage of calories from protein was significantly greater in the PRO-BEV group compared with the FAT-BEV group (week 2: PRO-BEV 42%, FAT-BEV 20%, $P = .05$; week 6: PRO-BEV 31%, FAT-BEV 14%, $P < .05$). Ghrelin, being orexigenic, increases in the absence of enteral intake and, in this study, was higher in the FAT-BEV group. Protein has been suggested to be the most satiating of the 3 macronutrients,⁹⁹ and perhaps a sustained reduced ghrelin level between meals is a mechanism for this. Because the study participants fasted for between 4 and 6 hours before the study, it might be more appropriate to consider them to be in a postprandial rather than fasting state. It is certainly possible that our levels of baseline fasting ghrelin were susceptible to some previous meal effects.

Although we observed an apparent difference between the treatment groups in fasting ghrelin concentrations at some of the postoperative time points, we hesitate to make general recommendations regarding the clinical significance and implication of these findings, for several reasons. First, we had a small sample size ($n = 8$ in each group) and might not have had enough power to detect real differences. Second, because this study was not originally designed to evaluate GI hormones, the fasting time period might not have been long enough to ensure an adequate preprandial state. Overall, we cannot be certain whether the difference in fasted ghrelin concentrations between groups was true or spurious, and thus further work is needed to elucidate the GI hormone profile in response to different macronutrients in the post-RYGB patient population.

Specific Findings—Fat Beverage Group

GLP-1 AUC was greater at 6 weeks and 1 year post-RYGB in the FAT-BEV group compared with baseline levels. Other research has investigated GLP-1 between 4 weeks^{9,78,100,101} and 6 weeks^{41,42,51,78,102} post-RYGB, and overall, and the findings were

similar to ours. Most researchers have found significantly increased levels at this time point compared with baseline,^{41,42,51,100,101} although 2 studies did not find such an effect.^{9,102} Clements et al¹⁰² may not have found increased GLP-1 at 6 weeks post-RYGB because they only measured the GI hormone in the fasted state, and GLP-1 is released in response to nutrient intake. The changes that we and others observed occurred when patients were still considered obese; therefore, the weight loss is not driving the changes in GLP-1. Instead, increased GLP-1 levels post-RYGB are thought to occur because of a surgical component that promotes more rapid delivery of nutrients to the distal gut.^{103,104}

The increased GLP-1 AUC levels found at week 6 were maintained long term in our study (ie, 1 year post-RYGB). Few other studies have evaluated GLP-1 changes at this specific time point post-RYGB. Korner et al⁷ found GLP-1 increased significantly at 1 year post-RYGB compared with baseline, whereas Morínigo et al⁴² did not find this. Increased GLP-1 levels have been found at post-RYGB in studies of longer duration (eg, >1 year) compared with those who underwent other weight loss procedures^{11,48,50} and nonsurgical controls,^{10,11,49,50,105} and this alteration has been hypothesized to play a role in the success of the procedure. le Roux et al⁴¹ evaluated those who had “good” and “poor” weight loss outcomes, defined as 40% and 20% weight loss after RYGB, respectively (RYGB was preformed 25.3 ± 1.7 months before the study). Patients considered to have poor weight loss had significantly lower GLP-1 levels compared with those who were considered to have good weight loss.⁴¹

In contrast to the lack of significant change in GLP-1 AUC levels in the PRO-BEV group from baseline to all time points following surgery, we found that GLP-1 AUC levels were increased in response to short-term administration of fat at 6 weeks and 1 year post-RYGB. This was a novel finding, as no other study to our knowledge has looked at GLP-1 changes in response to different macronutrients before and after RYGB. We found no significant differences at any of the time points between the groups in GLP-1 AUC. Graphic representation of the data suggests that the short-term response to protein was not stimulatory of GLP-1, and there might have been a difference between groups that we were unable to detect because of an insufficient sample size. Although it has been reported that both protein and fat can potently stimulate GLP-1 release, fat has been reported to stimulate GLP-1 more potently than protein in normal-weight individuals²⁸ and obese boys.²⁹ Lipids are thought to be the most potent stimulus for GLP-1 secretion, and ingestion of fats leads to sustained secretion.¹⁸ From our data in the RYGB patient population, fat ingestion more potently stimulated GLP-1 compared with protein. More work is needed in this area to establish the most effective post-RYGB diet recommendations.

Fasted GLP-1 levels were significantly greater at 6 months compared with baseline in only the FAT-BEV group. This result was unexpected, and we evaluated the macronutrient content of the meal eaten 4 to 6 hours before the baseline blood draw in order to better understand the mechanism involved. Compared with either protein or carbohydrate, fat most potently slows GI transit.¹⁰⁶ In addition, GLP-1 secretion peaks after meal termination and remains elevated for several hours afterward.^{11,48–51,78,100,101,105} Although both protein^{30,31} and fat^{28,29} stimulate GLP-1 secretion, it is possible that the FAT-BEV group had an elevated GLP-1 level secondary to the meal eaten before the visit, which was higher in the

percentage of calories from fat compared with the PRO-BEV group and might not have been completely digested and absorbed because of the slower transit time of fat (FAT-BEV 46% vs PRO-BEV 33%).

At 1 year post-RYGB, PYY AUC increased significantly compared with baseline levels. Studies that have specifically looked at this time point have reported similar findings.^{7,47} Likewise, cross-sectional studies that compared PYY levels in pre-RYGB patients,¹⁰⁷ other weight loss surgical patients,^{11,48} and nonsurgical controls^{10,11,44,45, 48} with those of patients who were at least 1 year post-RYGB found higher PYY in the post-RYGB group. It is thought that increased PYY levels, similar to GLP-1, mediate the long-term weight loss/maintenance found in RYGB patients. In the le Roux et al⁴¹ study that classified post-RYGB patients according to their weight loss outcome, those who were considered to have good weight loss had significantly higher PYY compared with the poor weight loss group.

This is the first study we know of that evaluated the PYY response after different macronutrients in the pre-RYGB and post-RYGB patient population. We found that at 1 year post-RYGB, PYY AUC only increased in response to the short-term administration dose of fat. Prior work evaluating the PYY response to different macronutrients in normal-weight individuals found that PYY is secreted in response to fat^{33,34} and protein,³⁶ and we are not sure why we did not see such an effect at 1 year for protein in our study. PYY AUC in the PRO-BEV group reached its peak at 6 months and by 1 year had decreased to a value similar to what was seen at week 2. Based on these results, we suggest that PYY is more sensitive to fat in the post-RYGB patient population, but more research in this area is needed before a definitive conclusion can be made.

Limitations

Several limitations need to be considered when evaluating our results. First, we had a small sample size ($n = 8$ in each treatment group) and might not have had enough power to detect real differences. Second, our study sample included only Caucasian women, and therefore, the findings are not generalizable to the population. Third, because of cost and time constraints, participants were not able to serve as their own controls for the 2 treatments, and instead they received only 1 beverage type for all 5 visits. Fourth, this analysis was part of a larger study evaluating body composition changes in the RYGB patient population and was not initially designed to evaluate leptin and the GI hormones. Consequently, participants in this study were only fasted for 4 hours before the baseline blood draw for GI hormones and leptin. The possibility of altered results secondary to the meal eaten 4 hours before the analyses cannot be ruled out.

Conclusions

We have shown that, in addition to substantial weight loss, multiple changes in GI hormones and leptin occur after RYGB. Some differences were evident quite soon after surgery (2 weeks: ghrelin, leptin) whereas others were maintained long-term (1 year: GLP-1, PYY, ghrelin, and leptin). Overall, the success of the procedure was likely attributable to the synergistic effect of these changes. To our knowledge, this is the first study to evaluate the effect of different macronutrients on GI hormones in the post-RYGB patient population.

Significant differences between macronutrient groups in terms of GI hormones and leptin were evident for ghrelin and leptin. In addition, differences were observed within treatment groups. Notably, we found that protein suppressed ghrelin, whereas fat was a potent stimulator of GLP-1 and PYY. This line of research has particular relevance to nutrition support practitioners because it may facilitate improvements in the nutrition care of post-RYGB patients. Future work in this area has the potential to better define post-RYGB macronutrient recommendations to impart greater satiety and thereby promote more effective weight loss and/or weight maintenance in this growing patient population.

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Clinical Relevancy Statement

Alterations in gastrointestinal hormones and leptin occur after Roux-en-Y gastric bypass (RYGB) surgery, and in some instances, they can be macronutrient-specific. From a clinical perspective, this is useful information that might allow clinicians to make improved macronutrient recommendations for patients who have undergone RYGB. Future work is needed in this area to better define the optimal diet for the RYGB patient population.

Figure 1.
Body weight change from baseline visit. *Significantly different from baseline, $P < .05$.

Figure 2.

Glucagon-like peptide 1 (GLP-1) area under the curve change from baseline visit.

*Significantly different from baseline, $P < .05$.

Figure 3.
Peptide YY (PYY) area under the curve change from baseline visit. *Significantly different from baseline, $P < .05$.

Figure 4.

Ghrelin area under the curve change from baseline visit. *Significantly different from baseline, $P < .05$; ‡significantly different between groups, $P < .05$.

Figure 5.

Fasted glucagon-like peptide 1 (GLP-1) change from baseline visit. *Significantly different from baseline, $P < .05$.

Figure 6.

Fasted ghrelin change from baseline visit. *Significantly different from baseline, $P < .05$;

‡significantly different between groups, $P < .05$.

Figure 7.

Fasted leptin change from baseline visit. *Significantly different from baseline, $P < .05$;

‡significantly different between groups, $P < .05$.

Table 1

GI Hormone and Leptin Analysis Time Points for Baseline, Week 6, Month 6, and 1 year^a After Roux-en-Y Gastric Bypass Surgery.

Time			
0 Min	+30 Min	+60 Min	+90 Min
Leptin			
GLP-1	GLP-1	GLP-1	
PYY		PYY	PYY
Ghrelin		Ghrelin	Ghrelin

GI, gastrointestinal; GLP-1, glucagon-like peptide 1; PYY, peptide YY.

^a Analyses were conducted at baseline (ie, 30 to 70 days before Roux-en-Y gastric bypass surgery [RYGB]) and at 6 weeks, 6 months, and 1 year following RYGB.

Table 2GI Hormone and Leptin Analysis Time Points for Week 2^a

Time			
0 Min	+60 Min	+90 Min	+120 Min
Leptin			
GLP-1	GLP-1	GLP-1	
PYY		PYY	PYY
Ghrelin		Ghrelin	Ghrelin

GI, gastrointestinal; GLP-1, glucagon-like peptide 1; PYY, peptide YY.

^a Analyses were conducted 2 weeks following Roux-en-Y gastric bypass surgery.

Table 3Baseline Characteristics of Study Participants^a

Characteristic	Protein Beverage Group (n = 8)	Fat Beverage Group (n = 8)
Age, y	51 ± 7	47 ± 11
Weight, kg	124 ± 13	128 ± 15
Height, cm	166 ± 5	166 ± 4
Body mass index, kg/m ²	45 ± 5	47 ± 6

^aData are given as mean ± standard deviation. There were no statistically significant differences between treatments.