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Effects of Gastrogastric Fistula Repair on Weight Loss and Gut Hormone Levels

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Abstract

Purpose—Weight regain after gastric bypass (GBP) can be associated with a gastrogastric fistula (GGF), in which a channel forms between the gastric pouch and gastric remnant, allowing nutrients to pass through the 'old route' rather than bypassing the duodenum. To further understand the mechanisms by which GGF may lead to weight regain, we investigated gut hormone levels in GBP patients with a GGF, before and after repair.

Materials and Methods—Seven post-GBP subjects diagnosed with GGF were studied before and 4 months after GGF repair. Another cohort of 22 GBP control subjects without GGF complication were studied before and 1 year post-GBP. All subjects underwent a 50g oral glucose tolerance test and blood was collected from 0-120minutes for glucose, insulin, ghrelin, PYY_{3-36}, GIP, and GLP-1 levels.

Results—Four months after GGF repair subjects lost 6.0 ±3.9kg and had significantly increased postprandial PYY_{3-36} levels. After GGF repair, fasting and postprandial ghrelin levels decreased and were strongly correlated with weight loss. The insulin response to glucose also tended to be increased after GGF repair, however no concomitant increase in GLP-1 was observed. Compared to the post-GBP group, GLP-1 and PYY_{3-36} levels were significantly lower before GGF repair; however, after GGF repair, PYY_{3-36} levels were no longer lower than the post-GBP group.

Conclusions—These data utilize the GGF model to highlight the possible role of duodenal shunting as a mechanism of sustained weight loss after GBP, and lend support to the potential link between blunted satiety peptide release and weight regain.

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Author Contributions
Data collection: CO, KA, TC, GW, BL.
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Keywords

gastric bypass; gastrogastric fistula; GLP-1; PYY_{3-36}; ghrelin; weight loss

Introduction

Roux-en-Y gastric bypass surgery (GBP) has been reported to result in an approximate 30% weight loss with improvement and/or remission of obesity related co-morbidities, such as type 2 diabetes (T2DM), in approximately 40-80% of cases [1,2]. Weight regain has been described after GBP in approximately 20-35 % of cases, generally 2 years or more following surgery [3]. This weight regain can at times be associated with the formation of a gastrogastric fistula (GGF), a complication in which a channel forms between the gastric pouch and gastric remnant, allowing nutrients to pass through the remnant and proximal intestine (ie-'old route'), rather than bypassing these, as is observed with GBP [4] (Figure 1).

The mechanism of sustained weight loss after GBP is not fully understood, however, enhanced release of gut satiety peptides is implicated. The shunting of the proximal small intestine (i.e.-foregut hypothesis) and accelerated nutrient transit to the distal small intestine (i.e.-hindgut hypothesis) both appear to contribute to the enhanced release of satiety peptides such as peptide YY (PYY) and glucagon-like peptide-1 (GLP-1) after GBP [5-8]. In addition, the absence of a rise in circulating levels of the orexigenic hormone ghrelin after GBP, observed in the early few months after the surgery [9], could explain the additional benefit of decreased food intake and weight loss early after GBP. GGF, once a fairly common occurrence after open GBP surgery, occurs now more rarely, at a rate of about 1-2% due to the use of improved bariatric laparoscopic techniques [10].

Although GGF is no longer a major post-operative concern, it presents a rare opportunity to study the endocrine mechanisms of weight gain and/or diabetes relapse in post-GBP patients. We hypothesized that subjects who developed a GGF would have a pattern of gut peptide release similar to that of pre-GBP patients, while the post-GGF repair condition would be similar to the post-GBP state with respect to weight loss, improved glucose homeostasis and pattern of gut hormone release.

Materials and Methods

Subjects

A total of 31 patients participated in this study. Nine patients, diagnosed with GGF post-GBP, enrolled in the GGF COHORT. One patient could not be contacted after GGF repair and another had poor IV access, therefore only 7 women from this cohort completed the study, two of whom had T2DM. The diagnosis of GGF was documented by upper endoscopy and/or Gastrografin studies by the surgical team.

Twenty-two participants (2 men and 20 women) with successful weight loss and no complications were studied before and 1 year after GBP and served as CONTROLS.

The study was approved by the St. Luke's-Roosevelt Hospital Center Institutional Review Board and all participants provided written informed consent prior to enrollment in the study.

Study Design

Surgical procedures

GBP surgery: All patients underwent a laparoscopic GBP with a 30-ml gastric pouch, 40-cm afferent limb, 150-cm Roux limb, and 12-mm gastrojejunostomy.

GGF repair: Patients with GGF underwent laparoscopic GGF repair. Intraoperative endoscopy confirmed the presence of the GGF. Linear cutting staplers were used to resect the body of the remnant stomach and the fistula tract and revise the gastric pouch. Repeat endoscopy and air insufflation confirmed the absence of any leak.

Oral glucose tolerance test (OGTT)—All participants underwent a 2 hour OGTT before and after GGF repair (GGF COHORT, average 4 months after GGF repair), or before and 12 months after GBP (CONTROLS). At each study visit, after an overnight fast, body weight was recorded on a precision scale, height measured, and BMI calculated. During the OGTT, blood was drawn from an IV catheter under fasting conditions and at 15, 30, 60 and 120 minutes after ingestion of 50 g of glucose (in 200 mL of non-carbonated water), for measurement of circulating concentrations of glucose, insulin, ghrelin, PYY_{3-36}, GIP, and total GLP-1.

Assays

Glucose was measured using the glucose oxidase method (glucose analyzer; Analox Instruments USA, Lunenberg, MA). Insulin, total ghrelin, PYY_{3-36}, and total GLP-1 were measured by radio-immuno assay (RIA) and GIP by enzyme-linked immunosorbent assay (ELISA) (Millipore, St. Charles, MO) in the Hormone and Metabolite Core laboratory of the Obesity Nutrition Research Center.

Statistical Analysis

Statistical analyses were performed with SPSS 19 (SPSS Inc., Chicago). Paired t-tests were used to assess longitudinal changes within groups and Spearman correlation was used to assess relationships between variables. Two-hour total AUC was calculated with the trapezoidal method. Data distribution was checked for normality. Data are presented as mean ± SD and the level of significance was $p<0.05$. Independent samples t-tests were used to compare GGF COHORT with the CONTROLS.

Results

Controls

Controls (n=22), age 45.0±9.2 years, with a pre-operative BMI of 45.7±6.5 kg/m^2, lost 38.2±11.5 kg at 12.6±1.7 months post-GBP. Fasting glucose and insulin and glucose AUC_{0-120}, decreased significantly, while fasting ghrelin, ghrelin nadir, ghrelin AUC_{0-120}, GLP-1 AUC_{0-120}, and PYY_{3-36} AUC_{0-120} all increased significantly 1 year after GBP (Table 1 and Figure 2).

GGF Cohort

Prior to surgery, self-reported BMI in the GGF cohort was 51.7±14.2 kg/m^2, which was not significantly different than pre-GBP BMI in the control group. Self-reported maximum weight loss after GBP was 58±31.7 kg (n=7). The main symptom that prompted the diagnosis of GGF was weight regain, reported in 4/7 subjects. Subjects regained 15.7±5.6 kg (calculated from self-reported minimum weight) 57±23 months after GBP. Characteristics of subjects are shown in Table 1. In patients post-GGF repair, weight loss resumed, with a total weight loss of 6.0±3.9 kg ($p=0.006$) over 4.1±4.0 months (range 2-13 months). BMI

decreased significantly from 36.9±7.6 kg/m^2 to 34.6±7.2 kg/m^2 (p=0.008). In patients post-GGF repair, $PYY_{3\text{-}36}AUC_{0\text{-}120}$ increased significantly (p=0.010), however the enhanced PYY3-36 response to oral glucose in patients post-GGF repair did not correlate with weight loss (r=-0.143, p=0.760). Neither GLP-1 nor GIP response to oral glucose was altered in patients post-GGF repair (Table 1), compared to pre-GGF repair, and these were not correlated with weight loss.

As predicted, circulating fasting ghrelin concentrations decreased in patients post-GGF repair by approximately 30% (p=0.004), as did ghrelin $AUC_{0\text{-}120}$ (p=0.006) and ghrelin nadir (p=0.016) (Table 1). Both fasting (r=0.857, p=0.014) and nadir (r=0.857, p=0.014) ghrelin concentrations strongly correlated with the amount of weight loss in patients post-GGF repair.

There was a 26% increase in the insulin response to oral glucose in patients post-GGF repair, that tended to be significant (p=.09) (Table 1). There was a non-significant decrease in fasting and glucose $AUC_{0\text{-}120}$, and HOMA-IR after GGF repair. Two patients who had T2DM at the time of the diagnosis of GGF had marked reductions in fasting glucose levels (from 12.3±1.2 mmol/L to 6.8±0.9 mmol/L) and 120 min glucose (from 14.4±2.2 mmol/L to 9.9±4.2 mmol/L) after GGF repair, with a mean weight loss of 9.4±0.7 kg. Neither fasting nor AUC glucose or insulin were correlated with weight loss

Comparison of the GGF cohort with the Controls

There was no significant difference in body weight between the controls pre-GBP compared to patients pre-GGF repair, or between the controls post-GBP compared to patients post-GGF repair (Table 1). Pre-GGF repair patients differed significantly from controls both pre-GBP and post-GBP on a number of parameters. The pre-GGF repair group had significantly lower BMI, fasting insulin and HOMA-IR and significantly higher GLP-1 $AUC_{0\text{-}120}$ (Table 1), and peak GLP-1 (56.6±27.1 pmol/L vs. 15.7±12.1 pmol/L, p=0.007) than the controls pre-GBP. Patients pre-GGF repair were heavier than controls post-GBP (BMI 36.9 ± 7.6 $kg{\cdot}m^{-2}$ vs. 31.3 ± 4.1 $kg{\cdot}m^{-2}$, p=0.018) and had a 58% and 35% lower GLP-1 and $PYY_{3\text{-}36}$ response to oral glucose, respectively (GLP-1 $AUC_{0\text{-}120}$ 22.8 ± 6.5 pmol/L/min vs. 54.6 ± 44.0 pmol/L/min, p=0.003; $PYY_{3\text{-}36}$ $AUC_{0\text{-}120}$ 69.3 ± 28.3 pmol/L/min vs. 106.0 ± 35.1 pmol/L/min, p=0.047) (Table 1). As expected post-GGF repair, ghrelin $AUC_{0\text{-}120}$ (p=0.033), nadir (p=.016) and fasting (p=.059) levels were lower than post-GBP controls. Unexpectedly, the GLP-1 response to oral glucose, which was lower in the patients pre-GGF repair, compared to post-GBP controls, remained significantly lower in patients post-GGF repair (p=0.006). There was no change in magnitude of the GLP-1 peak (56.6±27.1 pmol/L vs. 54.8±22.1 pmol/L, p=0.752) in the post-GGF repair group compared to pre-GGF repair. Contrary to GLP-1 levels, $PYY_{3\text{-}36}$ $AUC_{0\text{-}120}$ levels post-GGF repair were no longer significantly different from the post-GBP controls (p=0.169).

As a proxy for liquid gastric emptying (GE), we measured the time to reach peak serum glucose and the time to reach peak serum GLP-1 during the 2-hr OGTT. The post-GBP controls experienced an earlier peak glucose (64.1±19.2 min vs. 38.9±15.1 min, p<0.001) and peak GLP-1 (33.4±25.7 min vs. 17.7±5.9 min, p=0.010) one year after surgery compared to pre-GBP. However, GGF repair did not significantly decrease the time to peak glucose (pre GGF vs. post-GGF, 32.1±13.5 min vs. 34.3±11.3 min, p=0.356) or the time to peak GLP-1 (30.0±15.0 min vs. 23.6±8.0 min, p=0.448), although a non-significant trend was evident in the latter. There was a significant difference in time to peak glucose between the pre-GGF repair and pre-GBP (32.1±13.5 min vs. 64.1±19.2 min, p<0.001) and no difference between the post-GGF repair and post-GBP (34.3±11.3 min vs. 38.9±15.1 min, p<0.408). There was no significant difference in time to peak GLP-1 between the GGF cohort compared to the GBP control cohort, during either the pre or post conditions.

Discussion

We hypothesized that 1) GGF repair would lead to weight loss; 2) GLP-1, GIP and PYY_{3-36} response to oral glucose would be blunted in patients pre-GGF repair and would increase after GGF repair to levels comparable to the post-GBP group; and 3) circulating ghrelin concentrations would decrease after GGF repair and be significantly lower than the post-GBP group. These expected gut peptides changes in the post-GGF repair group would be consistent with the foregut hypothesis as well as expected changes after a gastrectomy. Our data show that approximately 4 months after GGF repair, weight loss resumed and yielded favorable changes in satiety and orexigenic gut hormones. After GGF repair, subjects lost an average of 6 kg, resulting in weight and BMI values that were not significantly different from the post-GBP control group. There was a very slight non-significant increase in the anorectic hormone GLP-1 after GGF repair. However, GLP-1 levels in both the pre- and post-GGF repair group were significantly lower compared to the post-GBP controls and higher compared to the pre-GBP controls. Oppositely, PYY_{3-36}, another anorectic satiety hormone, was significantly increased after GGF repair and no longer significantly lower than the post-GBP control group. The increase in PYY_{3-36} after GGF repair lends support to the theory that GGF could short-circuit the hormonal effect of GBP, and that GGF repair restores some features of the expected post-GBP physiology. This hypothesis would purport an increase in GLP-1 levels after surgery as well, however no significant increase was observed. This is a puzzling observation, particularly since PYY_{3-36} levels were elevated after GGF repair. PYY_{3-36}, like GLP-1, is secreted from L-cells in the distal ileum, and this increased secretion in gut hormones from L-cells may be due to increased GE rates after GBP [11,12]. However, evidence suggests that in the GGF group, GE rates were already reduced to levels of the post-GBP controls, and GGF repair did not further accelerate GE. It is also possible that the lack of significance is due to the small number of subjects, as well as the variability observed with GLP-1 response over time [13]. Furthermore, we measured total, not active GLP-1, and although these are correlated, we cannot rule out that perhaps there is increased active GLP-1 [14].

After GGF repair, we also observed a reduction in fasting, nadir and postprandial levels of the orexigenic hormone ghrelin; in fact, ghrelin was significantly lower in the post-GGF repair group compared to the post-GBP controls. This was consistent with our hypothesis, as GGF repair required the surgical removal of the gastric remnant, and thus the removal of the majority of ghrelin-producing cells [15]. This could potentially provide an additional weight loss effect in addition to that from GBP surgery. This is similar to what has been previously reported in subjects undergoing GBP with gastric fundus resection. Ghrelin levels after this procedure were reduced up to 1 year after surgery, while subjects undergoing GBP alone had a transient decrease in ghrelin levels up to 3 months, and increase in levels by 1 year [16]. In our current study, ghrelin levels were significantly increased 1 year after GBP (pre-GBP vs. post-GBP), in proportion with weight loss, which is in agreement with what has been previously shown by our group and others [9,17,18]. Hence, the sustained weight loss observed in the GBP controls suggests that the changes in GLP-1 and PYY_{3-36} observed in the post-GBP group may play a role in promoting weight loss, but the change in ghrelin may not. Increased GLP-1 and PYY_{3-36} after GBP surgery is in agreement with other studies [19-21] . It is tempting to speculate that the increased levels of the anorectic hormone PYY_{3-36} and decrease in the orexigenic hormone ghrelin may, in part, play a role in the weight loss observed in the post-GGF repair group; however this is unclear as our data is observational.

There was some limited evidence for an improvement in glucose metabolism after GGF repair. There was a non-significant improvement in fasting glucose, glucose AUC, and HOMA-IR, and a non-significant increase in fasting insulin and insulin AUC. This trending

increase in insulin AUC was observed without a concomitant increase in the incretin GLP-1 after GGF repair. The lack of significance with respect to other glucose parameters is likely due to the small sample size with a mixed diabetes status. These improvements in glucose metabolism are likely due to the reduction in body weight observed after GGF, rather than the modest changes in incretins GLP-1 and GIP. Although PYY_{3-36} has been shown to improve insulin sensitivity in mice independently of weight [22], the results in primates and humans are mixed [23,24] and hence the increased PYY_{3-36} levels are likely not mediating the tendency for improved glucose metabolism in this study.

We [20] and others [25,26] have previously shown that an increase in GLP-1 after GBP is implicated in the improvement in glucose metabolism after surgery. In this study, only two individuals had T2DM prior to GGF repair, and although diabetes improved in these individuals, we cannot draw any definitive conclusions with such small numbers. Future studies in subjects before and after GGF repair could more carefully assess how rapidly diabetes improves after repair by examining glucose metabolism shortly after GGF repair, prior to any measureable amount of weight loss. Similarly, long term studies in post-GBP patients with GGF complications could help elucidate the mechanisms responsible for weight regain and diabetes relapse after GBP surgery.

Although numerous studies have shown enhanced incretin and PYY release after GBP [19-21,25-29], the mechanisms by which this occurs are not fully understood. Two potential theories referred to as the *foregut hypothesis* and the *hindgut hypothesis*, were initially described [5,6]. The foregut hypothesis suggests that favorable changes in glucose metabolism after bariatric surgery can be attributed to exclusion of the proximal small bowel, including the duodenum and part of the jejunum. This is supported by several animal and human studies which exclude nutrients from the proximal small bowel either via intestinal bypass, endoluminal sleeves or GBP. It has been shown that gastrojejunal bypass in the Goto-Kakizaki (GK) rat, a non-obese animal model with type 2 diabetes, improved glucose tolerance independently of weight loss [5,30]. Duodenal-jejunal exclusion via an endoluminal sleeve in rats also improved glucose tolerance and increased GLP-1 levels independent of weight loss [8]. In GBP patients, it was shown that a glucose load administered orally induced greater plasma insulin and gut hormone (GLP-1 and PYY) responses compared with glucose loading via a gastrostomy tube [31], and studies with an endoluminal sleeve in humans have reported improved glucose metabolism [32,33]. On the other hand, vertical sleeve gastrectomy (VSG), a purely restrictive procedure that removes the majority of the stomach but does not bypass any of the small intestine, has been shown to improve glucose metabolism independent of weight loss in both rodents [34] and humans [35,36], and increase GLP-1 to post-GBP levels [34-36]. Thus, data from VSG studies invalidate the foregut hypothesis as there is no proximal small bowel exclusion with this procedure. This suggests that other mechanisms may be responsible for the improvement in glycemic control and the rise in gut peptides after surgery.

The hindgut hypothesis suggests that rapid nutrient delivery to the distal ileum leads to increased GLP-1 and PYY, and beneficial effects on glucose metabolism, independent of weight loss [7,11,37,38]. In fact, ileal transposition to the proximal intestine has been shown to be equivalent to duodenal-jejunal bypass in improving glucose tolerance and increasing GLP-1 levels [7,39]. Studies highlighting GE, which is accelerated after liquid consumption in GBP patients [12,19,40], also support the hindgut hypothesis. In a case study, *McLaughlin et al* showed that meal administration via a gastrostomy tube directly into the gastric remnant ameliorated hypoglycemia as well as hypersecretion of GLP-1 and insulin in a post-GBP patient with neuroglycopenia [41]. *Hansen et al* observed that meal administration to post-GBP patients either orally (bypassing the gastric remnant and proximal intestine) or via a gastrostomy tube into the gastric remnant yielded similar effects

on glucose and GLP-1, suggesting that accelerated nutrient delivery plays a role in enhanced incretin response and improved glucose metabolism [42]. These pioneering studies in humans by McLaughlin and Hansen [41,42] are one of the first to directly investigate the impact of the route of nutrient delivery on gut hormone secretion in post-GBP subjects. Future studies using direct delivery of nutrients to different parts of the intestine are required to determine the impact of the route of nutrient delivery on gut hormone levels and weight and glucose parameters

Although this study utilizes a unique model to study the potential effects of a dual route of nutrient delivery on weight and glucose-related parameters as well as gut hormone levels, there are some limitations. Firstly, we do not have pre-GBP glucose or hormone levels in the GGF cohort, to ascertain that these cohorts were optimally matched prior to GBP surgery. However, we do have two major characteristics pre-GBP in the GGF cohort, weight and age, and these were not significantly different between the two cohorts prior to GBP surgery. Secondly, we cannot assume that GGF size and anatomy was consistent between subjects. While it would be interesting to correlate fistula size and hormone levels prior to GGF repair, we do not have this detailed information for all subjects. In a related example, although stoma diameter after GBP does not appear to influence the rate of GE [43], stoma diameter has been shown to be inversely correlated with weight loss after GBP [44]. We suspect that a larger GGF would be hypothesized to secrete more nutrients into the remnant stomach and thus dampen the expected increase in PYY and GLP-1 expected after GBP, which could contribute to weight re-gain. Thus, although these observations are unique and timely, they should we interpreted with recognition of their limitations.

GGF is a serious but rare complication of GBP surgery, occurring in less than 2% of subjects, with a greater incidence after undivided open GBP versus divided open or closed surgery [10,45]. GGF usually requires surgical repair with removal of the fistula and surrounding necrotic tissue, potentially resulting in a complete remnant gastrectomy and a decreased gastric pouch size [4,46,47]. This rare clinical complication may be accompanied with weight regain and/or diabetes relapse [10]. GGF occurrence is rare at our institution (estimated 1.3%, data not shown), and thus our study has a limited sample size and follow-up after GGF repair. However this model complication provides a unique, non-invasive opportunity to study the effects of a dual route versus single route of nutrient delivery on gut peptides, glucose and energy metabolism and has the potential to provide insight into the mechanisms of diabetes relapse and weight regain.

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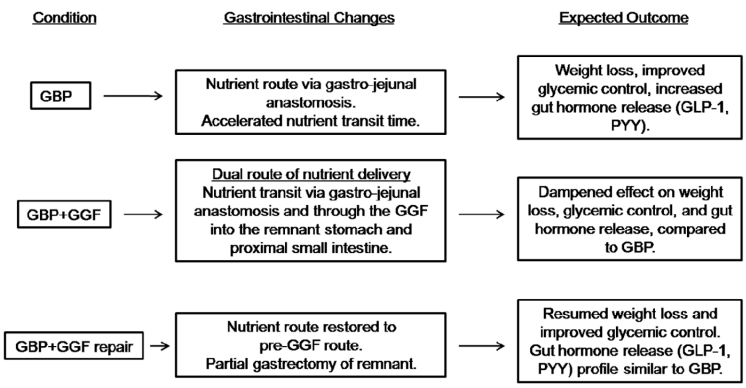

Fig. 1.
Gastrointestinal changes and expected metabolic and hormonal changes after GBP, GBP with a GGF, and GBP with a repaired GGF.

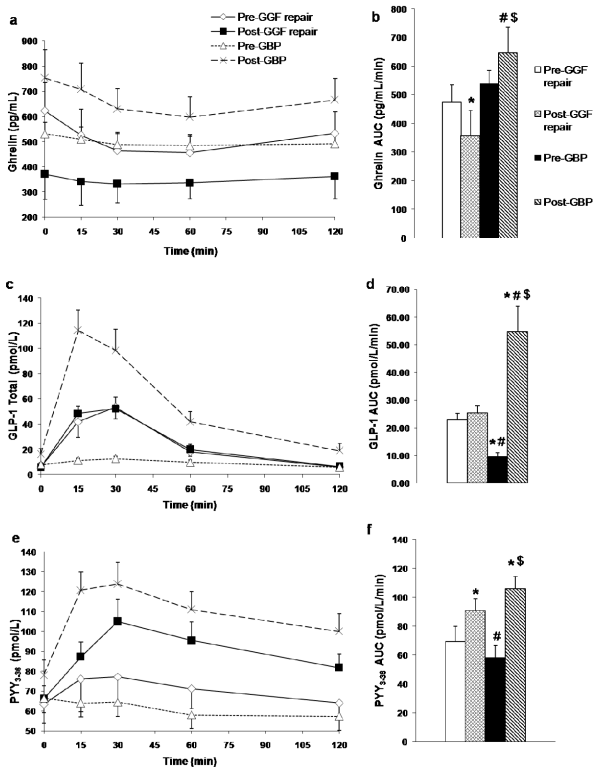

Fig. 2.

Gut Hormone Levels. Ghrelin (a,b), total GLP-1 (c,d), and PYY_{3-36} (e,f) levels during a 2-hr OGTT with AUC measurements. Significant differences are denoted by: * = p<.05 compared to Pre-GGF, # = p<.05 compared to Post-GGF, $ = p<.05 compared to Pre-GBP. n=7 for GGF, and n=22 for GBP controls. Data are mean ± SEM.

Table 1

Subject Characteristics, Glucose, and Hormone Levels

	Pre-GGF	Post-GGF	Pre-GBP	Post-GBP
Age (Years)	36.7±10.2		45.0±9.2	
BMI ($kg \cdot m^{-2}$)	36.9±7.6	34.6±7.2 *	45.7±6.5 *#	31.3±4.1 *$
Weight (kg)	101.5±33.6	95.4±33.2 *	120.5±20.0 #	82.3±13.5 *$
Fasting glucose ($mmol \cdot L^{-1}$)	6.8±3.8	5.4±1.1	7.4±2.4 #	4.9±0.7 $
Glucose $AUC_{0\text{-}120}$ ($mmol \cdot L^{-1} \cdot min^{-1}$)	9.4±6.0	8.1±3.4	10.8±3.0	7.7±1.7 $
Fasting insulin ($pmol \cdot L^{-1}$)	105.8±40.1	105.3±31.2	210.4±106.9 *#	70.6±32.7 *#$
HOMA-IR	4.8±3.9	3.7±1.6	9.5±5.9 *#	2.2±1.1 #$
Insulin $AUC_{0\text{-}120}$ ($pmol \cdot L^{-1} \cdot min^{-1}$)	396.2±157.7	500.1±194.2	479.3±274.0	447.9±251.6
Fasting ghrelin ($pg \cdot mL^{-1}$)	589.5±236.5	403.0±342.6 *	538.7±222.3	758.6±513.2 $
Ghrelin nadir ($pg \cdot mL^{-1}$)	425.4±141.8	300.0±190.2 *	493.9±206.1	590.3±367.7#$
Ghrelin $AUC_{0\text{-}120}$ ($pg \cdot mL^{-1} \cdot min^{-1}$)	474.0±162.3	357.3±231.9 *	538.5±204.6	646.5±391.4#$
GIP $AUC_{0\text{-}120}$ ($pg \cdot mL^{-1} \cdot min^{-1}$)	128.7±34.4	135.9±44.3	127.6±39.8	143.1±57.8
GLP-1$AUC_{0\text{-}120}$ ($pmol \cdot L^{-1} \cdot min^{-1}$)	22.8±6.5	25.5±6.3	9.5±7.1 *#	54.6±44.0 *#$
$PYY_{3\text{-}36}AUC_{0\text{-}120}$ ($pmol \cdot L^{-1} \cdot min^{-1}$)	69.3±28.3	90.9±21.2 *	58.2±34.7 #	106.0±35.1 *$

Values are mean ± SD.

* Significant differences are denoted by: = p<.05 compared to Pre-GGF,

= p<.05 compared to Post-GGF,

$ = p<.05 compared to Pre-GBP.

n=7 for GGF, and n=22 for GBP controls