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Journal Title: Obesity surgery ; the official journal of the American Society for Bariatric Surgery and of the Obes
Volume: 16 Issue: 7
Month/Year: 2006 Pages: 870-8
Article Author: Couce M; Cottam D; Esplen J; Schauer P; Burguera B
Article Title: Is ghrelin the culprit for weight loss after gastr

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ILL Number: 23452011

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Is Ghrelin the Culprit for Weight Loss after Gastric Bypass Surgery? A Negative Answer

Marta E. Couce; Daniel Cottam; James Esplen; Phillip Schauer; Bartolome Burguera

1Division of Endocrinology, 2Division of Neuropathology, 3Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Background: Ghrelin is a potent appetite stimulator, mainly synthesized in the stomach. Paradoxically, obese subjects have lower plasma ghrelin than lean subjects and increase their weight in spite of low ghrelin levels. The role of ghrelin in weight regulation after bariatric surgery is still controversial. The aim of this study was to evaluate whether rapid weight loss after laparoscopic Roux-en-Y gastric bypass surgery (RYGBP), was associated with changes in plasma ghrelin levels. In addition, we determined the acute impact of RYGBP on insulin resistance and adiponectin levels.

Methods: 49 morbidly obese subjects who underwent RYGBP were studied. 19 subjects who underwent other laparoscopic gastrointestinal surgeries acted as the control group. Fasting plasma levels of ghrelin, insulin and adiponectin were determined preoperatively and 2 hours, 10 days and 6 months postoperatively.

Results: At 2 hours after RYGBP, there was a significant reduction in ghrelin and adiponectin levels, which coincided with elevated plasma glucose and insulin levels. Interestingly, once glucose and insulin levels normalized at 6 months after surgery, ghrelin also normalized. Adiponectin reached pre-surgical levels at 10 days after RYGBP and continued to significantly rise until 6 months postoperatively.

Conclusion: Weight loss after RYGBP occurs in spite of the absence of significant changes in plasma ghrelin levels. Improvement of insulin resistance occurred within 10 days after surgery, and could be related to the normalization of adiponectin levels. This data questions the role of peripheral ghrelin as a cause of weight loss in obese humans after RYGBP.

Key words: Ghrelin, obesity, gastric bypass surgery, insulin, adiponectin, appetite

Introduction

Obesity is an epidemic, and in the U.S.A. 7 million individuals are classified as severely or morbidly obese.1,2 Complications of obesity include dyslipidemia, hypertension, type 2 diabetes mellitus, cardiovascular disease, obstructive sleep apnea, certain cancers, and degenerative joint disease.2,4 The NIH and international agencies have determined that bariatric surgery may be the only effective treatment for severely obese individuals.5 Laparoscopic Roux-en-Y gastric bypass (RYGBP) results in dramatic weight loss, with an average loss of 45 kg during the first 12 to 24 months.6-8 This substantial weight loss attained with bariatric surgery has major impacts upon the co-morbidities associated with obesity.5-10

Ghrelin is the endogenous ligand for the GH secretagogue receptor11 and also an important appetite-stimulating hormone.12-14 Ghrelin is produced predominantly by the stomach, but also in the hypothalamus.11,15-17 Ghrelin administration increases food intake in rats13,14 and in humans,18 and ghrelin levels are reduced in obese subjects.19-21 Other important peripheral signals, such as insulin and adiponectin, have been implicated in the regulation of appetite and plasma ghrelin levels.22,23 In obese humans, plasma adiponectin is low,24-26 and low levels of adiponectin have been proposed to contribute to insulin resistance associated with obesity.27 Hyperinsulinemia, which is usually associated with obesity, has been suggested to be responsible for the reduced ghrelin levels seen in obese individuals.28,29 Although the mechanism(s) by which RYGBP induces long-term weight loss are not well under-
stood, it has recently been hypothesized that reduction of circulating ghrelin may contribute to the success of weight loss after LRYGBP.30 Whereas several studies have shown that weight loss achieved after gastric bypass surgery was associated with decreased ghrelin levels,30-33 a significant number of studies have also described that circulating ghrelin remained unchanged34,35 or increased after gastric bypass surgery.34,36

In an effort to contribute to the better understanding of the specific role that ghrelin may play in the weight loss after gastric bypass, we have evaluated in a prospective study, the acute impact of LRYGBP on ghrelin, insulin and adiponectin in morbidly obese subjects.

Materials and Methods

In Vivo Studies

This study was carried out on 49 morbidly obese subjects (30 females and 19 males) who underwent LRYGBP for the treatment of morbid obesity at the University of Pittsburgh Medical Center (UPMC). The details of this surgery have been previously described.8 These patients had a mean age of 46.3 ± 2.2 years, mean weight of 142.2 ± 4.4 kg and mean BMI of 50.0 ± 5.3 kg/m². Twenty of these patients were on medical treatment for type II diabetes, 8 received oral therapy (metformin and sulfonylureas), and 12 were treated with oral therapy plus insulin. These patients were on a clear liquid diet 48 hours prior to surgery, and their diabetic medications were tapered or discontinued 24 hours prior to surgery. In addition, 19 subjects (9 females and 10 males), with a mean age of 56.6 ± 3.6 years, mean weight of 88.3 ± 7.1 kg and mean BMI of 29.8 ± 3.1 kg/m², who underwent other laparoscopic gastrointestinal surgeries (13 cholecystectomies and 6 inguinal hernias) at the UPMC by the same surgeons, acted as a control group. The exclusion criteria for the study included history of acute infection or injury, current or past history of chronic liver or kidney disease, history of congestive heart failure, current pregnancy, or substance abuse. Blood samples from both groups were collected 1 hour preoperatively, then 2 hours, 10 days, and 6 months postoperatively. Subjects were recruited from our Bariatric and Surgical Clinics at UPMC. All study procedures were in accordance with the Helsinki convention and approved by the University of Pittsburgh Institutional Review Committee. All blood samples were collected between 7 and 8 AM in the fasting state. Sera were centrifugally separated, aliquoted and stored at -70°C until being analyzed for levels of ghrelin, glucose, insulin, and adiponectin. Pre- and postoperative anthropometric measurements were obtained in all patients at different time points and are summarized in Table 1.

Hormonal Assay

Serum ghrelin was measured in duplicate, using a commercially available radioimmunoassay (RIA) for total ghrelin, according to the manufacturer's instructions (Phoenix Pharmaceuticals). Phoenix's human ghrelin RIA kit detects full-length, desoctanoyl human ghrelin, including Ser3-octanoyl and Ser-desoctanoyl ghrelin. Ghrelin intra- and inter-assay coefficients of variation (CoV) were: low=13.4, high=3.0 and low=8.7, high=7.2, respectively. Plasma adiponectin was measured using an RIA for human adiponectin (Linco Research) with intra- and interassay CoV low=6.1, high=5.7 and low=14.5, high=12, respectively. Insulin was measured with a human insulin-specific RIA kit (Linco Research) with intra- and inter-assay CoV low=4.3, med=2.4, high=3.8 and low=6.4, med=7.5, high=6.7, respectively. Plasma glucose was determined by the glucose oxidase method (Autoanalyzer, Beckman Coulter). Fasting plasma glucose and insulin levels were used to calculate the insulin resistance by the Homeostasis Model Assessment index (HOMA-IR). HOMA-IR was calculated as previously described36 using the formula: fasting serum insulin (U/ml) X fasting serum glucose (mmol/liter)/22.5.

Statistical Analysis

Results are expressed as mean ± SEM. Data is compared using a two-tailed, paired t-test (pre- vs postoperative) and two-sample Student’s t-test. Statistical analysis was performed using SigmaStat with significance set at P<0.05 and a power of >80%.
Table 1. Demographic characteristics and hormonal profile of surgery subjects

<table>
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<tr>
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<th>LRYGBP (n=49, 30 female)</th>
<th>Control (n=19, 9 female)</th>
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<tr>
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<td>Preoperative 2 Hours</td>
<td>Preoperative 2 Hours</td>
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<tr>
<td>Age (yr)</td>
<td>46.3 ± 2.2</td>
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<tr>
<td>Body Mass Index†</td>
<td>50.0 ± 5.3</td>
<td>29.8 ± 3.1</td>
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<tr>
<td>Ghrelin (pg/mL)</td>
<td>932.4 ± 52.2</td>
<td>713.3 ± 40.4**</td>
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<tr>
<td>Adiponectin (µg/mL)</td>
<td>9.0 ± 1.1</td>
<td>8.0 ± 1.1**</td>
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<tr>
<td>Insulin (µU/mL)</td>
<td>25.5 ± 3.2</td>
<td>35.2 ± 3.4*</td>
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<tr>
<td>Glucose (mg/dL)</td>
<td>101.9 ± 8.4</td>
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<tr>
<td>Ghrelin (pg/mL)</td>
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<td>Adiponectin (µg/mL)</td>
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<td>Insulin (µU/mL)</td>
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<td>Glucose (mg/dL)</td>
<td>107.8 ± 11.8</td>
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<td>HOMA Index</td>
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<td>Preoperative 6 Months</td>
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<tr>
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<td>Ghrelin (pg/mL)</td>
<td>802.3 ± 79.6</td>
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<td>7.9 ± 1.8</td>
<td>11.7 ± 1.5**</td>
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<td>Insulin (µU/mL)</td>
<td>23.7 ± 4.8</td>
<td>8.4 ± 0.82*</td>
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<tr>
<td>Glucose (mg/dL)</td>
<td>94.8 ± 10.3</td>
<td>86.2 ± 1.5*</td>
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<tr>
<td>HOMA Index</td>
<td>5.5 ± 0.7</td>
<td>1.8 ± 0.4**</td>
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Mean values (±SE) are shown.
+Age, 2 hour weight, and 2 hour BMI did not change from preoperative and are therefore not shown.
†Body Mass Index (BMI) is calculated as the weight of the patient in kilograms divided by the square of the patients' height in meters (kg/m²).
*Denotes (P<0.05) student's t-test
**Denotes (P<0.01) student's t-test

Results

Plasma Ghrelin Levels after LRYGBP

Fasting plasma ghrelin levels were measured in patients having LRYGBP and in obese control patients undergoing other laparoscopic abdominal surgeries, preoperatively and at 2 hours, 10 days and 6 months postoperatively. The preoperative plasma ghrelin was lower in the LRYGBP group compared to the control group (Figure 1). These results would be expected, given the higher BMI in the LRYGBP group (Table 1). At 2 hours postoperatively, there was a statistically significant drop in ghrelin levels in both the LRYGBP (P<0.001) and control groups (P<0.001). At 10 days after surgery, plasma ghrelin levels continued to be reduced in the LRYGBP group, whereas ghrelin levels had normalized in the control group. At 6 months after LRYGBP, morbidly obese patients had plasma levels of ghrelin that were not significantly different compared to pre-
surgery values ($P<$0.08). This happened in spite of significant weight loss in these patients, in whom BMI had by decreased 20% (Figure 1).

Plasma Glucose and Insulin after LRYGBP

Morbidly obese patients showed a mean plasma glucose which was significantly higher compared to the control surgical group ($P<$0.03) (Figure 2A). There were 20 patients with type 2 diabetes who had their oral medications discontinued 24 hrs prior to surgery. The mean plasma glucose significantly increased in both the LRYGBP ($P<$0.01) and control groups ($P<$0.001) when measured 2 hours after surgery, but this is not unexpected as patients were given intravenous infusion of 5% dextrose and 1/2 normal saline during surgery. Ten days after surgery, the mean plasma glucose in the LRYGBP group had dropped to normal values similar to the control group. Mean plasma glucose in the LRYGBP group continued to be normal 6 months after surgery. Mean pre-surgical insulin levels were significantly higher in the LRYGBP group compared to the control group ($P<$0.004). Insulin levels increased in both groups of patients 2 hours after surgery ($P<$0.03) (Figure 2B); however, only the LRYGBP group showed a significant increase when compared to baseline insulin levels. Ten days after surgery, insulin had significantly dropped in the LRYGBP group (36.4%) ($P<$0.001), reaching normal fasting levels. This insulin reduction in the LRYGBP group was even more pronounced at 6 months after surgery (64.7%) ($P<$0.01), coinciding with a normalization of ghrelin levels at this point (622.7 ± 59.4 pg/mL). There was a significant improvement in insulin sensitivity as measured by HOMA index at 10 days and 6 months after surgery (Table 1).

Plasma Adiponectin Levels after LRYGBP

Fasting plasma adiponectin was similar in both surgical groups before surgery. Our data showed a significant drop in plasma adiponectin at 2 hours after surgery in both the LRYGBP ($P<$0.004) and control ($P<$0.001) groups (Figure 2C). Adiponectin levels were back to within normal range for both groups at 10 days. At 6 months, plasma adiponectin in LRYGBP was significantly higher than the preoperative level ($P<$0.001). Interestingly, we noticed that the changes in plasma adiponectin concentration after LRYGBP were a virtual mirror image of plasma fluctuations for insulin.

Discussion

Our studies provide the first time-course record of plasma ghrelin changes over a 6-month period after LRYGBP. In agreement with previous studies, we noticed that plasma ghrelin was significantly lower in morbidly obese compared to lean subjects.19-21
Plasma ghrelin significantly fell 2 hours after LRYGBP. Interestingly, we saw a similar acute ghrelin drop in the control surgical group undergoing other gastrointestinal surgical operations. Plasma ghrelin continued to be low in the LRYGBP group 10 days after surgery, whereas they had almost returned to pre-surgical values by 6 months.

Ghrelin seems to be implicated, in both the regulation of appetite and body weight. However, there is still significant controversy in the literature regarding the role that ghrelin might play in the regulation of appetite in patients who have undergone bariatric surgery (Table 2). Contrary to what would be expected, plasma levels of this orexigenic hormone are lower in obese individuals compared to lean subjects, and circulating ghrelin increases under negative energy balance circumstances, such as low-calorie diets. Cummings et al. showed that plasma ghrelin was suppressed 9–31 months after gastric bypass surgery. Based on this early data, it has been suggested that the weight-reducing efficacy of gastric bypass surgery could be partially explained by its effect reducing circulating ghrelin levels. Similarly, Tritos et al. showed that serum ghrelin was lower in obese subjects 18 months after gastric bypass surgery, compared to obese subjects.
Table 2. Impact of the different types of bariatric operations on plasma ghrelin levels (GBP: Gastric bypass, BPD: Billipancreatic diversion, GB: Gastric banding, LSG: Laparoscopic sleeve gastrectomy, VBG: Vertical banded gastropasty, NC: no change)

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<td>Langer</td>
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<tr>
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In response to an oral glucose tolerance test. In addition to these two cross-sectional studies, Geloneze et al. described in a prospective study, that the mean plasma ghrelin levels decreased significantly after surgery in obese non-diabetics and obese type 2 diabetic subjects, 12 months after gastric bypass surgery. Frühbeck et al. also showed that LRYGBP caused a significant reduction in ghrelin levels in morbidly obese patients 6 months after the surgery. The acute impact of gastric bypass surgery on plasma ghrelin levels was also evaluated by Morinigo et al. who measured plasma ghrelin in eight morbidly obese patients before and 6 weeks after LRYGBP. These authors found that, despite a significant weight loss, fasting serum ghrelin was decreased in obese subjects 6 weeks after LRYGBP.

In contrast to these studies, Faraj et al. showed in a prospective study, that circulating ghrelin did not decrease 6 months after gastric bypass surgery. In fact, plasma ghrelin increased postoperatively in the subset of subjects undergoing active weight loss, whereas ghrelin remained unchanged in weight-stable subjects. Holdstock et al. also reported that serum ghrelin significantly increased (by +58%) 12 months after RYGBP. In agreement with these studies, Kornr et al. showed that fasting plasma ghrelin was nearly identical between subjects who had undergone RYGBP and matched controls. Supporting these studies, Stoeckli et al. found that plasma ghrelin levels did not change during substantial weight loss 24 months after RYGBP.

The discrepancies among these different studies (Table 2) may be partially explained by analyzing three different issues. The first variable that needs to
be taken into consideration is the difference in follow-up time after the gastric bypass operation. It seems that short-term follow-up after LRYGBP is associated with acute reductions of plasma ghrelin as suggested by Morinigo et al.\(^3^8\) Lin et al.\(^4^1\) and our studies (6 weeks, 1 day and 10 days after surgery, respectively). However, the long-term follow-up data collection after surgery (>3 months) varies among the different studies published (Table 2). Our studies showed that plasma ghrelin levels were not significantly different when measured 6 months after LRYGBP, in agreement with Faraj et al.\(^3^4\) and Holdstock et al.\(^3^5\).

Secondly, it has been shown that weight loss in obese individuals is associated with increasing plasma ghrelin levels. Cummings et al.\(^3^0\) showed that a diet-induced weight loss of 17% of initial body weight, was associated with a 24% increase in the area under the curve for the 24-hour ghrelin profile in obese subjects. However, 5% weight loss had no effect on plasma ghrelin levels in obese subjects that followed 3 weeks of an integrated weight loss program.\(^4^2\) These findings could explain why we see low ghrelin levels 10 days after LRYGBP, when there is still little weight loss, compared to the higher ghrelin levels at 6 months after surgery when patients have lost between 10-30% of their original body weight. LRYGBP seems to be causing reduction of ghrelin levels; however, active weight loss “normalizes” plasma ghrelin.

Thirdly, the small variants within the gastric bypass surgical technique, such as the size of the gastric pouch, length of the Roux limb and additional vagotomy, may also be partially responsible for the differences in ghrelin levels documented in the published studies. Interestingly, truncal vagotomy is known to cause reduced food intake and weight loss in humans, and ghrelin administration did not stimulate food intake in patients with surgical procedures involving vagotomy.\(^4^3\) Regardless of what is the explanation(s) responsible for these conflicting data, a clear evidence emerges from all these studies (Table 2): morbidly obese patients lose weight after undergoing gastric bypass regardless of their plasma ghrelin levels after surgery.

The notion that variations in ghrelin concentrations may have little impact on causing weight loss after gastric bypass is further supported by three different sets of studies: The first evidence comes from morbidly obese subjects who underwent laparo-

scopic adjustable gastric banding (LAGB). Several studies have shown that adjustable silicone gastric banding (ASGB) caused significant weight loss, in spite of causing an increase in plasma ghrelin concentrations after the operation.\(^3^3,4^4,4^6\) It seems that changes in eating behavior, which promote reduction of food intake and not fasting ghrelin levels, determine weight loss achieved by adjustable gastric banding. Studies modifying the degree of band restriction around the stomach, showed that optimal LAGB restriction increased fasting and postprandial satiety. However, plasma ghrelin levels appeared unrelated to the LAGB satiety effect.\(^4^7\)

A second set of evidence comes from studies using another bariatric surgical procedure, the Scopinaro biliopancreatic diversion (BPD). Adami et al.\(^4^8\) showed similar serum ghrelin concentrations before and 2 months following BPD, whereas plasma ghrelin increased significantly 1 year after BPD.\(^4^8,4^9\) Lastly, if ghrelin were to play a significant role in the weight loss after bariatric surgery, it would be expected that the amount of weight lost after gastric bypass should correlate with plasma ghrelin levels. Interestingly, Christou et al.\(^5^0\) showed that the failure to lose weight after gastric bypass surgery did not correlate with pre- or post-prandial plasma ghrelin. They also reported that ghrelin levels did not correlate with satiety. Taken together, these different studies question the role of ghrelin as the main culprit for weight loss after RYGBP.

In addition to ghrelin, we also evaluated the impact of LRYGBP surgery on plasma insulin and adiponectin. Several lines of evidence suggest that insulin may regulate the production of ghrelin. Insulin concentrations are higher in obese individuals with insulin resistance, whereas ghrelin levels are low. Insulin administration has also been shown to decrease ghrelin concentrations in humans.\(^2^8,2^9\) In addition, the changes in plasma insulin concentrations, before and after meals, are a virtual mirror image of fluctuations in ghrelin concentrations.\(^5^1\)

Our studies show that there is a significant elevation of plasma insulin levels 2 hours after LRYGBP surgery, which is associated with low ghrelin and adiponectin levels. Interestingly, plasma insulin levels like ghrelin, normalized at 6 months after surgery. A similar situation occurred with adiponectin, which also normalized at 10 days after surgery and continued to significantly rise at 6 months after surgery.
Adiponectin therapy has been associated with improvement of insulin resistance\textsuperscript{2,53} and reduction of appetite. To what degree this reduction in insulin after LRYGBP could be responsible for the maintenance of weight loss, rise of adiponectin and improvement of insulin sensitivity, is a matter of great interest which deserves further studies. Adami et al.\textsuperscript{48} showed a negative correlation between the postoperative changes of serum ghrelin concentration and insulin sensitivity 2 and 12 months after BPD. Based on our results, we hypothesize that insulin has a possible causal role in modulating ghrelin and adiponectin secretion after LRYGBP surgery. Further studies are necessary to investigate whether a negative energy balance or changes in other gastrointestinal hormones, such OGL or PYY, could also be involved in the normalization of plasma insulin soon after bariatric surgery and before a significant weight loss has been accomplished.

In summary, our study shows that weight loss after LRYGBP occurs in spite of the absence of significant changes in plasma ghrelin levels. This data seriously questions the potential role of ghrelin as responsible for the weight loss after bariatric surgery.

We thank the John F. & Nancy A. Emmerling Fund of The Pittsburgh Foundation and The University of Pittsburgh Obesity and Nutrition Research Center for their generous financial support.

References

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(Received February 2, 2006; accepted April 29, 2006)