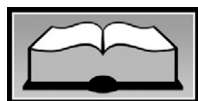


Review



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Changes in Gastrointestinal Hormones and Leptin after Roux-en-Y Gastric Bypass Procedure: A Review

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ABSTRACT

Roux-en-Y gastric bypass is a well-accepted tool for the treatment of obesity and, compared to conventional weight loss methods (eg, diet and exercise) and other weight loss surgeries (eg, gastric banding), it results in considerable weight loss that is maintained long term. Although successful, the mechanisms for weight loss are not completely understood and it is thought that gastrointestinal hormones play a role. Several gastrointestinal hormones have been identified for their effects on appetite, including glucagon-like peptide-1 (GLP-1), peptide tyrosine-tyrosine (PYY), leptin, and ghrelin. This review encompasses a literature search that included 45 primary articles and shows that there are alterations in GLP-1, PYY, leptin, and ghrelin postoperatively. GLP-1 and PYY concentrations were usually found to be higher, whereas ghrelin levels were typically lower post-Roux-en-Y gastric bypass than in individuals with obesity, those who were overweight or of normal weight, and in those who underwent procedures other than Roux-en-Y gastric bypass or who achieved weight loss by lifestyle modification. An understanding of how gastrointestinal hormones change after Roux-en-Y gastric bypass may help dietetics practitioners optimize nutrition care for this patient pop-

ulation. A review of the literature also highlighted some research gaps that should be taken into consideration when designing future studies.

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Roux-en-Y gastric bypass (RYGB) is a well-accepted tool for the treatment of obesity and, compared to conventional weight loss methods (eg, diet and exercise) and other weight loss surgeries (eg, gastric banding), it results in considerable weight loss that is maintained long term. Although successful, the mechanisms for weight loss are not completely understood and it is thought that surgery-induced changes in gastrointestinal hormones play a role. It is important for registered dietitians to have an understanding of how gastrointestinal hormones change after RYGB so that they can improve nutrition care in this patient population. The purpose of this review is to report the relevant literature regarding changes in gastrointestinal hormones after RYGB.

OVERVIEW OF THE RYGB PROCEDURE

Overweight and obesity are worldwide epidemics, and it is estimated that more than 1.5 billion adults are overweight (body mass index [BMI] ≥ 25), with 600 million being classified as obese (BMI ≥ 30) (1). By 2015, the World Health Organization estimates that more than 2.3 billion adults will be overweight and 700 million will be obese (1). Traditional weight loss therapies including low-energy diets, exercise, behavior therapy, and pharmacotherapy have been implemented; however, these methods have had little long-term success (2). Bariatric surgery is currently the only known method that offers both considerable and long-term weight loss (2). In fact, bariatric surgery is increasing in prevalence in the United States and worldwide due to the increasing rate of obesity; lack of effectiveness with traditional therapies; introduction of the laparoscopic method, which has made it less invasive to patients; increased media attention; and greater access to the therapy (3). There are several bariatric surgeries currently performed, including vertical banded gastro-

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Hormones	Mechanism of action
Glucagon-like peptide-1 (GLP-1)	Secretion of GLP-1 reduces hunger and imparts satiety by: <ul style="list-style-type: none"> ● Slowing gastric emptying (12,16) ● Promoting insulin release (16) ● Inhibiting glucagon secretion (16) ● Inhibiting gastric acid secretion (12) ● Acting on the central nervous system (17-20)
Peptide YY (PYY)	Secretion of PYY reduces hunger and imparts satiety by: <ul style="list-style-type: none"> ● Delaying gastric emptying (26) ● Inhibiting gastric acid secretion (26)
Leptin	Secretion of leptin decreases food intake and increases energy expenditure by: <ul style="list-style-type: none"> ● Acting on the hypothalamus (13,32,33)
Ghrelin	Secretion of ghrelin stimulates appetite by: <ul style="list-style-type: none"> ● Increasing gastrointestinal motility (11,35) ● Decreasing insulin secretion (11,35)

Figure 1. Overview of hormones. NOTE: Information from this figure is available online at www.adajournal.org as part of a PowerPoint presentation.

plasty, gastric banding, sleeve gastrectomy, biliopancreatic diversion, duodenal switch, and RYGB.

RYGB is the safest and most efficacious bariatric surgery and, thus, it is currently the most commonly performed operation, comprising about 70% to 75% of all bariatric procedures (2). It can be performed using either open or laparoscopic techniques, with laparoscopic being the preferred method due to its quicker recovery time and decreased postoperative complications (4,5). Weight loss is thought to be equivalent between the two methods, as the primary difference between open and laparoscopic RYGB is the method of access (2). RYGB is classically described as having both malabsorptive and restrictive components. With this procedure, the distal stomach, duodenum, and proximal jejunum are bypassed (4). The restrictive component is achieved by creating a small gastric pouch, which promotes early satiety (3,4) and thereby decreases intake (3).

During the RYGB gastric bypass surgical procedure, the distal jejunal limb is connected to the new gastric pouch, creating a Roux limb (2), also known as the alimentary limb that functions to transport nutrients (3). Roux limbs vary in length, and typically range from 75 to 150 cm (2,3). Although these physiological modifications are thought to be a primary reason for the RYGB's success, it is also important to consider the contribution of gastrointestinal hormones and neural pathways to the process (3). Indeed, there is a growing body of evidence that favorable changes in several gastrointestinal hormones may have a substantial role in the weight loss seen after RYGB (6,7). Furthermore, Borg and colleagues (6) have suggested that the observed alterations in gastrointestinal hormones may represent an adaptive response to offset the physiologic modification created by the RYGB procedure.

GASTROINTESTINAL HORMONES AND LEPTIN IN NORMAL PHYSIOLOGY

Several gastrointestinal hormones have been identified for their effects on appetite, including glucagon-like peptide-1 (GLP-1), peptide tyrosine-tyrosine (PYY), leptin,

and ghrelin (Figure 1). Although detailed reviews are available elsewhere describing the characteristics of these hormones (8-16), a brief overview on how these hormones affect appetite in normal physiological states follows here.

GLP-1

The incretin GLP-1 is secreted from the L cells in the distal ileum and colon in response to energy intake (8-11). There are two biological forms of GLP-1: GLP-1_{7-36amide} and GLP-1₇₋₃₇ with GLP-1_{7-36amide} being the most prevalent and active isoform (8). Consequently, future references to GLP-1_{7-36amide} in this review will be referred to as simply GLP-1.

GLP-1 is considered an appetite regulating hormone because secretion of it reduces hunger and imparts satiety (14). GLP-1 is secreted in response to either a mixed meal or individual nutrients such as carbohydrate, fat, protein, and fiber (10). The mechanism by which GLP-1 promotes satiety is thought to be multifaceted because it slows gastric emptying (12,16), promotes insulin release (16), inhibits glucagon secretion (16), inhibits gastric acid secretion (12), and acts on the central nervous system to induce satiety and decrease food intake (17-20). Because of these aforementioned effects, it is considered to play an important role in the ileal brake mechanism (17), which regulates the passage of nutrients through the gastrointestinal tract (21). The satiety-promoting effects of GLP-1 are evident when it is peripherally administered, as it has been found to reduce appetite and energy intake in healthy weight humans (22) as well as those with obesity (23); consequently, it has been investigated as a therapy for weight loss. Given the mechanism of action of GLP-1 it would be expected that postprandial plasma levels would be elevated in normal weight individuals and lower in those with obesity, and there are some data to support this (24); however, there are conflicting findings (25).

PYY

Similar to GLP-1, PYY is secreted from the L cells of the gut after a meal (8,11,13,16). It occurs in two forms:

PYY₁₋₃₆ and PYY₃₋₃₆, with PYY₃₋₃₆ being the major circulating form (13). Unless otherwise noted, reference to PYY₃₋₃₆ in this review will be notated as PYY. PYY is also considered an appetite-regulating hormone given that secretion of it reduces hunger and imparts satiety (14). One mechanism by which PYY is thought to promote satiety is through its role in the ileal brake (17). In other words, PYY delays gastric emptying and inhibits gastric acid secretion, as discussed in a review by le Roux and Bloom (26). Intravenous PYY infusion has been found to decrease energy intake and reduce hunger in healthy individuals (27) and those with obesity (28). It has been reported that fasting and postprandial PYY levels are lower in those with obesity and higher in normal weight individuals (28,29), but not all studies have found this to be true (30,31). As a result, it has been suggested that reduced PYY release is not likely to be a mechanism involved in the etiology of obesity (8,28).

Leptin

Since the discovery of leptin in 1994, a plethora of research has been conducted to establish its role in the pathogenesis of obesity. Leptin is a product of the obesity gene (*ob* gene) and is understood to be involved in long-term energy balance (32). It is secreted by adipocytes and influences energy intake primarily by acting on the hypothalamus (13,32,33) to decrease food intake and increase energy expenditure (33). Leptin circulates in proportion to whole-body adipose tissue mass (32). For example, increased body fat results in increased leptin, which ultimately stimulates reduced food intake, and the converse is also true with decreased body fat (32). However, increased leptin levels do not prevent obesity (13); therefore, it has been suggested that the progression of obesity is not a result of leptin deficiency but instead leptin resistance (33).

Ghrelin

Ghrelin is another appetite regulating hormone, although, unlike GLP-1, PYY, and leptin, it is the only known orexigenic (ie, appetite stimulating) hormone (8,9,11,13). Ghrelin circulates in two forms: active (acylated) and inactive (desacyl) (34). A majority of the studies presented here measured total ghrelin (both active and inactive forms) and, consequently, unless otherwise noted, total ghrelin will be notated as simply ghrelin.

The antisatiating properties of ghrelin may be due to its biological effects to increase gastrointestinal motility and decrease insulin secretion (11,35). It is released both centrally (pituitary) and peripherally (stomach) and energy intake may be the primary regulator of plasma ghrelin levels (14). Circulating ghrelin levels are increased during states of negative energy balance (36), including diet-induced weight loss in individuals with obesity (37) and decreased during feeding and in individuals with obesity (38). This mechanism has been postulated to be a protective response to stimulate energy intake in the underweight and to suppress it in the overweight (9). However, in obesity, ghrelin is not suppressed with food intake (39); therefore, this mechanism may be an important factor in the etiology of obesity or it may

actually be a consequence of obesity that results from chronic overfeeding.

METHODS

This review encompasses a literature search in the English language that yielded 100 primary articles. A comprehensive literature search was conducted using Ovid Medline with the following search query: “Roux-en-Y OR gastric bypass,” which was then run against “GI hormones OR hormones OR GLP-1 OR PYY OR leptin OR ghrelin.” Additional articles were identified from bibliographies of recent review papers. Articles were excluded if the study design included one or more of the following characteristics: use of animal models as the study population; utilization of a surgical technique that did not include RYGB; not differentiating between surgery type in analyses; failure to measure one or more of the following hormones: GLP-1, PYY, leptin, or ghrelin; case-study design; and inclusion of subjects that had previous weight loss surgeries. After applying the aforementioned exclusion criteria, 45 articles were identified and reviewed.

Each study was evaluated for its strength in research methodologies. For studies investigating GLP-1, PYY, and ghrelin, a study was considered strong if it included either a control group (eg, obese, lean, or other surgical procedure) and/or sampled for the gastrointestinal hormone at multiple time points after consumption of a meal. In terms of the latter, it is advantageous to sample at multiple time points after food intake (eg, sample at baseline and then every 30 minutes for 3 hours) to capture the gastrointestinal hormone response to a meal. However, for leptin, it is common to sample once and/or in the fasted state since it has been found to be unaffected by meal consumption as it primarily is a reflection of adipose mass (40). Therefore, in terms of the reviewed leptin literature, a study was considered to be strong if it included a control group.

GLP-1 Changes after RYGB

In the studies that utilized a control group (41-49) and/or sampled at multiple time points (6,41-47,50) (Figure 2), the data concerning GLP-1 after RYGB is consistent. In studies that compared RYGB patients to nonsurgical patients who were lean, overweight, or with obesity, all but one study (43) found that GLP-1 levels were significantly higher after RYGB (41,42,45,47,49). To control for the effects of weight loss on GLP-1 changes, the aforementioned studies weight-matched the participants to the pre-RYGB weight (eg, subjects who have obesity) (41,43,45,47) and/or the post-RYGB weight (eg, overweight subjects) (41,42,49). Even when weight-matched, RYGB patients had significantly different GLP-1 values compared to either subjects who have obesity or are overweight. Moreover, one would expect that lean individuals would have higher GLP-1 values compared to RYGB subjects; however, the one study that compared post-RYGB subjects to lean subjects did not indicate this at 6 to 36 months post-op when subjects were still considered to have obesity (45), suggesting that a component of the RYGB procedure alters the GLP-1 profile.

Hormones measured	Limb length	Study groups	Time points	Measurements	Summary
Studies of strong design: prospective/retrospective, controlled					
Ghrelin (78)	75 cm for BMI ^a <50 and 150 cm for BMI ≥50	Group 1: RYGB (n=49, 30 F); Group 2: obese who underwent other laparoscopic GI ^b surgeries (eg, cholecystectomies, inguinal hernias) (n=19, 9 F)	1-h pre-op and 2-h, 10-d, and 6-mo post-op	Fasted blood samples collected	<ul style="list-style-type: none"> ● 2-h post-op plasma ghrelin significantly lower in both groups compared to pre-op ● 10-d post-op plasma ghrelin significantly lower in only RYGB group compared to pre-op ● 6-mo post-op plasma ghrelin not significantly different from pre-op levels in either group
Ghrelin (80)	100 cm for BMI <45 and 140 cm for higher BMI	Group 1: RYGB (n=10; 9 female [F]); Group 2: VBG ^c (n=12, 11 F)	Pre-op and when subject achieved 20% reduction in BMI (131±6 d for RYGB and 119±4.2 d for VBG)	Blood collected 45 min before 504-kcal liquid test meal, and 5 min after meal, and every 60 min for 3 h	<ul style="list-style-type: none"> ● Plasma ghrelin significantly higher in post-VBG group than in obese pre-op or in post-RYGB group ● Plasma ghrelin significantly lower in post-RYGB group compared to obese pre-op ● No fluctuations in plasma ghrelin pre- or post-RYGB
Ghrelin, leptin (61)	Not reported	Group 1: RYGB (n=6); Group 2: AGB ^d (n=7); Group 3: BPD ^e (n=3); study n=16; 7 F	Pre- and 6.1±0.4 mo post-op	Fasted blood samples collected	<ul style="list-style-type: none"> ● No significant differences in BMI, body fat, EWL^f, or body fat loss between 3 groups ● Significantly lower fasting plasma ghrelin in RYGB group compared with other groups ● Significant decrease in post-op leptin in all 3 groups, but no statistical differences between groups
Ghrelin, leptin (62)	Not reported	Group 1: RYGB (n=8, 0 F); Group 2: AGB (n=8, 0 F); Group 3: conventional weight loss non-surgical matched for BMI (n=8, 0 F); Group 4: total gastrectomy (n=6, 0 F)	Pre-op and 6 mo post-op	Fasted blood samples collected	<ul style="list-style-type: none"> ● Significant reduction in weight, BMI, and body fat at post-op in AGB, RYGB, and conventional weight loss groups ● Post-op weight and BMI significantly higher in RYGB group compared to total gastrectomy group ● Significantly lower fasting post-op plasma ghrelin in RYGB and total gastrectomy groups ● At post-op, significantly lower fasting plasma ghrelin in RYGB and total gastrectomy group compared to AGB and conventional weight loss groups ● At post-op, no significant differences in fasting plasma ghrelin between RYGB and total gastrectomy groups, despite significant body weight and BMI differences
Ghrelin, PYY (60)	150 cm	Group 1: RYGB (n=16, 12 F); Group 2: LSG ^g (n=16, 15 F)	Pre-op and 1, 3, 6, and 12 mo post-op	Fasted blood samples collected and in a subset of the study group, blood was collected 2 h after 420-kcal mixed meal	<ul style="list-style-type: none"> ● Weight loss and BMI not significantly different between RYGB and LSG groups at 12 mo post-op ● EWL significantly greater in LSG group at 6- and 12-mo post-op compared to RYGB group ● Fasting ghrelin not significantly different at any time point in the RYGB group but significantly decreased in the LSG group compared to pre-op ● Fasting PYY^h significantly increased post-op in both groups ● In subset of LSG and RYGB subjects who were evaluated pre- and post-meal, postprandial PYY significantly increased at pre-op in LSG group and at 3-, 6-, and 12-mo post-op in both groups ● In subset of LSG and RYGB subjects who were evaluated pre- and post-meal, postprandial ghrelin significantly decreased at all time points in LSG group only
Active and total GLP-1 (43)	150 cm	Group 1: RYGB (n=8), Group 2: obese (n=7); male (M) and F included but sex totals not reported	Pre-op and 1 mo post-op	50 g OGTT ⁱ completed after 12-h fast; Blood collected at baseline and every 5 min for 3 h after OGTT	<ul style="list-style-type: none"> ● At the end of OGTT (180 min) total GLP-1 AUC^j significantly greater at post-RYGB compared to pre-op ● Total GLP-1^k significantly higher post-RYGB compared to pre-RYGB at 15, 30, and 45 min of the OGTT ● Active GLP-1 significantly higher at 15 min of the OGTT post-RYGB compared to pre-RYGB levels
Active and total GLP-1 (44)	150 cm	Group 1: RYGB (n=9, 9 F); Group 2: diet-induced weight loss, matched for age, weight, BMI, diabetes duration and control (HbA1c ^l) to RYGB (n=10, 10 F)	Group 1: pre-op and 1 mo post-op; Group 2: pre- and post-10 kg diet-induced weight loss	Blood drawn after 50 g OGTT on 2 different days, separated by less than 5 d; blood collected at baseline and every 15 min for the first 90 min and then every 30 min until 180 min	<ul style="list-style-type: none"> ● Weight not statistically different between groups after either diet or surgical induced weight loss ● Peak total GLP-1 significantly increased from pre- to post- RYGB ● Peak active and total GLP-1 significantly higher in post-RYGB group compared to post-diet group ● Total GLP-1 AUC significantly increased from pre- to post-op ● Total GLP-1 AUC significantly greater in post-RYGB group compared to post-diet group ● Active GLP-1 AUC significantly increased from pre- to post-op ● Active GLP-1 AUC significantly higher in post-RYGB group compared to post-diet group ● At post-RYGB, total GLP-1 significantly higher at 15, 30, and 45 min of the OGTT compared to pre-RYGB, pre-diet, and post-diet groups ● At post-RYGB, active GLP-1 significantly higher at 15 min of the OGTT compared to pre-RYGB, pre-diet, and post-diet groups

(continued)

Hormones measured	Limb length	Study groups	Time points	Measurements	Summary
Ghrelin (82)	100-150 cm	Group 1: RYGB (n=34); Group 2: VBG (n=4); Group 3: obese ARS™ (n=4); Group 4: lean ARS (n=6); sex characteristics not reported	Pre-op and 30-min post-op	In all groups, plasma collected 30 min before and after surgery; in RYGB group, plasma also collected before surgery, 10 min after transecting the jejunum, 10 min after completely dividing the stomach to form the small vertical pouch, and post-op (no timeframe provided)	<ul style="list-style-type: none"> ● Ghrelin significantly higher in lean ARS compared to pre-RYGB ● Significant decrease in ghrelin at post-RYGB compared to pre- ● Significantly lower ghrelin in post-RYGB compared to lean ARS ● In RYGB: the time points "stomach" (after dividing the stomach to create the small pouch) and "post-op" had significantly lower ghrelin compared to pre-op
Leptin (68)	Not reported	Group 1: RYGB (n=15, 15 F); Group 2: lean (n=10, 10 F)	Pre-op and 6 mo post-op	Fasted blood samples collected	<ul style="list-style-type: none"> ● Significantly higher leptin in pre-RYGB group compared to lean group
Leptin (63)	Not reported	Group 1: RYGB (n=29, 29 F); Group 2: non-obese (n=13, 13 F)	Pre-op and 1, 3, 6 mo post-op	Blood samples collected before meal and after overnight fast	<ul style="list-style-type: none"> ● At all time points post-RYGB, leptin significantly decreased compared to the previous time point; leptin significantly lower at 6 mo compared to baseline
Ghrelin, leptin (64)	100 cm	Group 1: RYGB (n=8; 5 F); Group 2: healthy normal weight matched for age (n=6, 3 F)	8 wk pre-op and 6 wk post-op	Fasted blood samples collected pre-398 kcal mixed liquid meal and at 10-, 30-, 60-, and 120-min post-meal	<ul style="list-style-type: none"> ● BMI in RYGB group decreased significantly at 6 wk ● Fasting plasma ghrelin significantly lower in pre-RYGB compared with lean controls ● Ghrelin AUC decline significantly higher in control subjects compared to pre-RYGB subjects; no significant difference between pre- and post-RYGB ghrelin AUC ● Post-RYGB fasting ghrelin significantly lower compared to pre-RYGB ● Individual responses to meal highly variable at both pre- and post-RYGB ● At post-RYGB, no significant correlations found between percentage weight loss and change in either fasting ghrelin or ghrelin AUC
Ghrelin, PYY (59)	150 cm	Group 1: RYGB (n=25, 6 F); Group 2: healthy normal weight matched for sex and age (n=6, 2 F); Group 3: severely obese with type 2 diabetes (n=10, 5 F)	RYGB subjects: pre-op and 6 and 52 wk post-op; Subset of RYGB group (those in upper and lower %EWL quartile): pre-op, 6, and 52 wk, and 32.5±1.1 mo post-op; Normal weight controls: one time point	Fasted blood samples collected pre-398 kcal mixed liquid meal and at 10-, 30-, 60-, 90-, and 120-min post-meal	<ul style="list-style-type: none"> ● Postprandial PYY AUC response significantly increased at 6 wk post-op ● PYY response in RYGB subjects significantly greater compared to normal weight healthy controls ● Subjects in upper quartile of the %EWL distribution at 6 wk post-op had significantly higher PYY response AUC compared with those in lower quartile ● At 32.5±1.1 mo post-op, PYY AUC was significantly larger in those with larger weight loss ● Fasting plasma ghrelin significantly decreased 6 wk post-op ● At 52 wk, plasma ghrelin returned to levels comparable to baseline and were significantly greater than those observed at 6 wk post-RYGB ● Significant inverse correlation between fasting PYY and fasting plasma ghrelin at 6 wk post-op ● Lower fasting plasma ghrelin at 6 wk post-op significantly associated with greater weight loss at 32.5±1.1 mo
Active GLP-1 and total PYY (47)	Not reported	Group 1: RYGB (n=9; 7 F); Group 2: obese matched for sex, age, and BMI (n=6, 4 F)	Pre-op and 6 wk post-op	Fasted blood samples collected pre-398 kcal mixed liquid meal and at 10-, 30-, 60-, 90-, and 120-min post-meal	<ul style="list-style-type: none"> ● Pre-RYGB, postprandial total PYY or active GLP-1 did not significantly increase after meal ● Significant weight lost at 6 wk post-RYGB ● Post-op active GLP-1 significantly increased at 30- and 60-min post-meal compared to pre-meal ● Post-op total PYY significantly higher at 30-, 60-, 90-, and 120-min post-meal compared to pre-meal ● Neither GLP-1 or PYY were correlated with weight loss at post-RYGB ● GLP-1 and PYY response to meal significantly greater in post-RYGB than in obese
GLP-1, PYY (48)	Not reported	Group 1: RYGB (n=19, 84% F); Group 2: GB ^a (n=11, 91% F)	Pre-op and 2 y post-op	Fasted blood samples collected	<ul style="list-style-type: none"> ● RYGB lost significantly more weight than GB group ● PYY increased significantly in both groups post-op; not significantly different between groups ● GLP-1 decreased significantly in both groups post-op; Post-op GLP-1 significantly lower in RYGB compared to GB group

(continued)

Figure 2. Summary of research reviewed in a study of changes in gastrointestinal hormones and leptin after Roux-en-Y gastric bypass (RYGB). NOTE: Information from this figure is available online at www.adajournal.org as part of a PowerPoint presentation.

Hormones measured	Limb length	Study groups	Time points	Measurements	Summary
Leptin (67)	Not reported	Group 1: RYGB (n=30, 27 F); Group 2: LAGB ^o (n=10, 8 F)	Pre-op and 1 yr post-op	Fasted blood samples collected	<ul style="list-style-type: none"> Leptin significantly decreased post-op in both groups; did not differ between groups
Ghrelin, leptin (65)	75 cm	Group 1: RYGB (n=5); Group 2: ASGB ^P (n=8); Group 3: obese (n=7); gender characteristics not reported	Pre-op and 3, 6, 12, 24 mo post-op	Fasted blood samples collected	<ul style="list-style-type: none"> BMI decreased significantly in both RYGB and ASGB groups compared to controls during 24 mo BMI significantly lower in RYGB compared to ASGB at 6 months Plasma leptin significantly lower in both ASGB and RYGB groups compared to control at 24 mo Plasma ghrelin significantly increased in ASGB group compared to control at 24 mo Changes in ghrelin significantly and negatively correlated with change in BMI in all groups (when analyzed together) Changes in ghrelin significantly and negatively correlated with change in BMI in ASGB group but not RYGB (when analyzed separately) Change in plasma leptin positively correlated with change in BMI in all groups
Prospective, uncontrolled					
Leptin (76)	Not reported	Pre-RYGB vs. post-RYGB (n=20, 20 F)	Pre op and 3, 6, and 12 mo post-op	Fasted blood samples collected	<ul style="list-style-type: none"> Leptin significantly reduced post-RYGB
Ghrelin, leptin, GLP-1, PYY (6)	112 cm	Pre-RYGB vs. post-RYGB (n=6); sex characteristics not reported	Pre-op and 1-, 3-, 6-mo post-op	Fasted blood samples collected and after 420-kcal mixed meal, and 15- and 30-min later, and at 30-min intervals for 3 h	<ul style="list-style-type: none"> Fasting leptin and postprandial PYY AUC significantly decreased at 3 and 6 mo post-op Postprandial GLP-1 AUC significantly higher at 6 mo post-op
GLP-1 (53)	150 cm	Pre-RYGB vs. post-RYGB (n=20, 15 F)	Pre-op and 2-, 6-, and 12-wk post-op	Fasted blood samples collected	<ul style="list-style-type: none"> Weight significantly reduced at 12-wk post-op No significant changes in GLP-1 at any time points compared to pre-op
Leptin (71)	Not reported	Pre-RYGB vs post-RYGB (n=68, 39 F)	Pre-op and every 1 to 2 mo during first year post-op and every 3 mo thereafter for 2 y	Fasted blood samples collected	<ul style="list-style-type: none"> At time of maximum weight loss (15±4 mo), plasma leptin decreased significantly
Leptin (74)	Not reported	Pre-RYGB vs post- RYGB (n=30, 24 F)	Pre-op and 1 y post-op	Fasted blood samples collected	<ul style="list-style-type: none"> Leptin significantly decreased from pre- to post-RYGB
STUDY 1: Ghrelin, GLP-1, PYY (46)	STUDY 1: 100 cm for BMI <50 and 150 cm for BMI >50	STUDY 1: pre-RYGB vs post-RYGB (n=16, 11 F)	STUDY 1: pre-op and 2-, 4-, 7-, and 42-d post-op	STUDY 1: Blood sample collected in fasted state and right after 400-kcal mixed meal, and at 15 min and 30 min post-meal and every 30 min for 3 h post-meal	STUDY 1: <ul style="list-style-type: none"> PYY AUC significantly different at 2-, 4-, and 42-d post-RYGB GLP-1 AUC significantly different at all days post-RYGB; significant increases occurred as early as Day 2 and continued to rise until Day 42
Ghrelin (83)	Not reported	Pre-RYGB vs. post-RYGB (n=10, 10 F)	Pre-op and 6-mo post-op	Fasted blood samples collected and then every 20 min for 24 h; subjects provided with 4 meals/d with fixed energy level	<ul style="list-style-type: none"> No significant difference in pre-prandial or postprandial ghrelin pre- or post-op
GLP-1 (50)	Not reported	Pre-RYGB vs post-RYGB (n=34, 23 F)	8 wk pre-op and 6 wk and 12-mo post-op	Fasted blood samples collected pre 398-kcal mixed liquid meal and at 10-, 30-, 40-, 50-, 60-, 90-, and 120-min post-meal	<ul style="list-style-type: none"> GLP-1 AUC significantly increased 6 weeks post-op compared to baseline values in subjects with normal glucose tolerance
Leptin, GLP-1 (54)	100 cm	Pre-RYGB vs post-RYGB (n=10, 9 F)	Pre-op and 3-wk post-op	Fasted blood samples collected	<ul style="list-style-type: none"> Leptin significantly lower at post-op compared to pre-GLP-1; not significantly different between pre- and post-op
Ghrelin, PYY (84)	70 cm	Pre-RYGB vs post-RYGB (n=15, 14 F)	2-wk pre-op and 1-, 2-, 4-, and 6-d and 1-, 6-, and 12-mo post-op	Fasted blood samples collected	<ul style="list-style-type: none"> Ghrelin decreased post-RYGB but then increased and was above baseline values at 1-mo and continued to increase throughout follow-up (significance not reported)
Leptin (73)	Not reported	Pre-RYGB vs post-RYGB (n=19, 19 F)	Pre-op and 1-, 3-, 6-, and 12 -mo post-op	Fasted blood samples collected	<ul style="list-style-type: none"> Leptin significantly lower at all time points compared to pre-op Change in fat mass significantly related to change in leptin
Desacyl and active ghrelin, GLP-1 (55)	150 cm	Pre-RYGB vs post-RYGB (n=10, 9 F) (5 diabetics and 5 nondiabetics)	Pre-op and 6-mo post-op	Fasting state and blood collection timing unspecified	<ul style="list-style-type: none"> Normalized GLP-1 significantly increased in nondiabetic group at post-op Normalized inactive, desacyl ghrelin significantly increased in nondiabetic group at post-op No significant changes in active ghrelin in either group from pre- to post-RYGB

(continued)

Figure 2. Continued

Hormones measured	Limb length	Study groups	Time points	Measurements	Summary
Leptin (75)	Not reported	Pre-RYGB vs. post-RYGB (n=10: 9 F) (5 diabetics and 5 nondiabetics)	Pre-op and 6 months post-op	Fasting state and blood collection timing unspecified	<ul style="list-style-type: none"> ● Significant decrease in normalized leptin post-RYGB in both diabetics and nondiabetics
Ghrelin, leptin (66)	Not reported	Pre-GBP vs post-GBP (n=34, sex characteristics not reported)	Pre-op and 24-wk post-op	Fasted blood samples collected before meal and after overnight bed rest	<ul style="list-style-type: none"> ● Post-GBP^a, ghrelin significantly increased ● Post-GBP, leptin significantly decreased
Cross-sectional, controlled					
Ghrelin, PYY (56)	Not reported	Group 1: RYGB (n=6, 3 F); Group 2: obese (n=12, 7 F); Group 3: lean (n=5, 4 F)	1.5±0.7 y post-op	75g OGTT (350 kcal) completed after 12-h fast; Blood collected at baseline, 30-, 60-, 90-, 120-, and 180-min after OGTT	<ul style="list-style-type: none"> ● In RYGB group, at 30-, 60-, and 90-min, postprandial PYY significantly greater compared to fasting levels ● In RYGB group, PYY peaked at 30 min and remained significantly elevated compared to fasting levels until 90 min ● Significantly greater PYY at all time points after fasting in RYGB group compared to lean and obese groups ● Ghrelin significantly higher in lean than in obese and RYGB ● Ghrelin significantly higher in lean compared to the other two groups ● No significant differences in pre- and postprandial plasma ghrelin in either RYGB groups ● Significant inverse correlation between pre-op BMI and preprandial plasma ghrelin
Ghrelin (77)	150 cm	Group 1: RYGB with unacceptable weight loss (BMI >35) (n=16, 14 F); Group 2: RYGB with acceptable weight loss (BMI <35) (n=20, 18 F); Group 3: lean (n=8, 6 F)	3-5 y post-op	4-h fasting blood sample collected post-breakfast; 600-kcal lunch provided and 4 h later, second blood sample collected	<ul style="list-style-type: none"> ● Dietary weight loss group lost significant amount of weight ● Significant leptin reduction in dietary weight loss group ● Temporal ghrelin pattern of circulating ghrelin levels similar before and after dietary weight loss ● After weight loss in the dietary weight loss group, ghrelin increased at every time point during the 24-h measurement period ● Mean ghrelin AUC significantly increased after weight loss in dietary weight loss group ● In dietary weight loss group, significant positive correlation between percentage decrease in either body weight or BMI and the percentage increase in ghrelin AUC ● Ghrelin AUC significantly lower in RYGB group compared to other groups ● Ghrelin profile of RYGB group not similar to meal-related oscillations nor the diurnal rhythm seen in normal weight and obese controls (flat pattern seen in RYGB group)
Ghrelin, leptin (37)	Not reported	Group 1:RYGB (n=5, 3 F); Group 2: normal weight (n=10, 9 F); Group 3: obese who had lost weight through conventional methods and were matched for final RYGB weight (n=13, 8 F)	RYGB: 9 to 31 mo post-op; weight loss group: after weight loss	Fasted blood samples collected and every 30 min between 8 AM and 9 PM, then hourly until 8 AM (24 h). Breakfast, lunch, dinner served at 8 AM, 12:00, and 5:30 PM	<ul style="list-style-type: none"> ● Fasted ghrelin significantly higher in RYGB group compared to obese controls ● Morbidly obese group had no or a blunted postprandial ghrelin response ● Similar meal-induced suppression of ghrelin in RYGB and young nonobese group and this suppression was significantly larger than what was seen in morbidly obese
Ghrelin (79)	50 cm	Group 1: middle-aged morbidly obese (n=10, 5 F); Group 2: middle-aged RYGB (n=10, 5 F); Group 3: middle-aged nonobese (n=10, 5 F); Group 4: young nonobese (n=10, 5 F)	RYGB: 42.5±11.1 mo post-op; dietary-induced weight loss group: before and after weight loss	Fasted blood collected at 0800, 1000, 1200, 1300 h; 770-kcal meal provided at 1300 and post-meal blood collected at 1330, 1400, 1430, 1500, and 1600	<ul style="list-style-type: none"> ● Body weight not statistically different between post-RYGB and normal weight controls ● Fasting leptin significantly lower in post-RYGB group compared to normal weight controls ● Fasting GLP-1 significantly higher in RYGB with NG compared to RYGB without NG ● Postprandial GLP-1 significantly higher in RYGB with NG than RYGB without NG at 30-, 60-, and 120-min post-meal ● GLP-1 significantly higher after RYGB compared to nonsurgical controls ● Significantly higher leptin in morbidly obese compared to all other study groups
Leptin (70)	Not reported	Group 1: RYGB (n=8, 8 F); Group 2: normal weight (n=8, 8 F)	2 to 3 y post-op	Fasted blood samples collected	<ul style="list-style-type: none"> ● Leptin significantly lower post-RYGB compared to control subjects both in absolute terms and per unit of fat mass
GLP-1, leptin (41)	Not reported	Group 1: RYGB with NG ^r (n=12, 10 F); Group 2: RYGB without NG (n=9, 7 F); Group 3: overweight (n=10, 4 F); Group 4: morbidly obese (n=5, 5 F)	Post-op only (3.3±1.6 y RYGB with NG and 2.8±1.0 y RYGB without NG)	Fasted blood samples collected pre-liquid mixed meal (Ensure [®]) and at 10-, 20-, 30-, 60-, and 120-min post	<ul style="list-style-type: none"> ● Leptin significantly lower post-RYGB compared to control subjects both in absolute terms and per unit of fat mass
Leptin (69)	Not reported	Group 1: RYGB (n=6, 6 F); Group 2: obese (n=6, 6 F)	24 to 30 mo post-op	Fasted blood samples collected	<ul style="list-style-type: none"> ● Leptin significantly lower post-RYGB compared to control subjects both in absolute terms and per unit of fat mass

(continued)

Figure 2. Continued

Hormones measured	Limb length	Study groups	Time points	Measurements	Summary
PYY, total and octanoylated ghrelin, leptin (57)	150 cm	Group 1: RYGB (n=12, 12 F); Group 2: lean (n=8, 8 F); Group 3: BMI and age matched (to group 2) (n=12, 12 F)	35±5 mo post-op	Fasted blood samples collected and at 30-, 60-, 90-, 120-, and 180-min post-liquid 420-kcal meal	<ul style="list-style-type: none"> ● Post-op, 9 of 12 RYGB subjects still considered obese ● Total ghrelin maximal suppression response to meal similar between RYGB and lean and significantly lower in matched controls compared to lean ● Fasted octanoylated ghrelin significantly higher in lean controls compared to RYGB and matched controls ● Post-meal, early exaggerated rise in PYY in RYGB group ● Postprandial peak PYY significantly greater in RYGB compared to matched and lean controls ● PYY AUC significantly greater in RYGB at 90 min compared to lean and matched controls ● PYY AUC significantly greater in RYGB at 120 min compared to matched controls ● Leptin similar between lean controls and RYGB groups ● Leptin significantly higher in matched controls compared to other groups ● Leptin significantly correlated to BMI
Total PYY, PYY ₍₃₋₃₆₎ , total and octanoylated ghrelin, leptin (58)	100 to 150 cm	Group 1: RYGB (n=9, 9 F); Group 2: overweight (n=11, 11 F); Group 3: BND [†] (n=9, 9 F); Group 4: lean (n=8, 8 F)	26.7±1.5 mo post-op	Fasted blood samples collected before 320-kcal liquid meal, and at 30-, 60-, 90-, 120-, and 180-min post-op	<ul style="list-style-type: none"> ● Fasted total PYY, PYY₍₃₋₃₆₎ immunoreactivity, and total ghrelin not significantly different among groups ● Fasted octanoylated ghrelin higher in lean controls compared to overweight, BND, and RYGB groups ● Postprandial, early and exaggerated rise in total PYY and PYY₍₃₋₃₆₎ in RYGB group ● Magnitude of postprandial suppression of total ghrelin significantly blunted in BND and overweight groups compared to lean and RYGB groups ● Magnitude of postprandial suppression of octanoylated ghrelin significantly less in BND compared to RYGB group ● Fasting plasma leptin significantly higher in BND and overweight groups compared with lean controls and were significantly greater in overweight group compared to RYGB
GLP-1 (42)	100 to 150 cm	Group 1: RYGB (n=13, 13 F); Group 2: overweight (n=13, 13 F); Group 3: BND (n=10, 10 F)	24.6±2 mo post-op	Fasted blood samples collected before 320-kcal liquid meal, and at 30-, 60-, 90-, 120-, and 180-min post	<ul style="list-style-type: none"> ● RYGB group lost significantly more weight than BND group ● Significantly higher GLP-1 in RYGB compared to overweight and BND group at 30- and 60-min post-meal ● GLP-1 AUC significantly greater in RYGB group at 180 min compared to other groups
STUDY 2: PYY, GLP-1 (46)	STUDY 2: 100 cm for BMI <50 and 150 cm for BMI >50	STUDY 2: Group 1: good RYGB weight loss (n=13); Group 2: poor RYGB weight loss (n=7); sex characteristics not reported	STUDY 2: 25.3-mo post-op	STUDY 2: Fasted blood samples collected and right after 400-kcal mixed meal, and every 30 min for 3 h post-meal	<p>STUDY 2:</p> <ul style="list-style-type: none"> ● Post-meal, significantly higher PYY and GLP-1 in good weight loss group compared to those who had poor weight loss results
PYY, GLP-1, ghrelin (45)	112 cm	Group 1: RYGB (n=6, 6 F); Group 2: GB (n=6, 6 F); Group 3: obese (n=12, 9 F); Group 4: lean (n=15, 13 F)	6 to 36 mo post-op	Fasted blood samples collected before mixed 420-kcal meal, 15 min after, and at every 30 min for 3 h after meal	<ul style="list-style-type: none"> ● Fasting leptin significantly higher in RYGB, gastric band, and obese subject compared to lean ● Significantly higher postprandial GLP-1 response in RYGB compared to both fasting levels and other groups ● Similar GLP-1 response in gastric band compared to obese ● Postprandial PYY in RYGB significantly greater than fasting levels and lean ● PYY not different between gastric band and lean ● Fasting ghrelin not different between obese and RYGB and gastric band groups
Ghrelin (81)	40 cm	Group 1: RYGB (n=11, 8 F); Group 2: LASGB [‡] (n=10, 10 F); Group 3: obese matched for BMI to LASGB and RYGB (n=10, 7 F); Group 4: total gastrectomy (n=8, 2 F); Group 5: normal weight (n=8, 4 F)	9 to 15 mo post-op	Breakfast at 0900 and lunch at 1300; plasma collected before and after breakfast and lunch at 0900, 1000, 1100, 1300, 1400, 1500	<ul style="list-style-type: none"> ● No significant differences in BMI between RYGB and LASGB groups ● Significantly lower ghrelin in RYGB group compared to LASGB, normal weight, and obese ● Significantly lower plasma ghrelin in total gastrectomy group compared to all other groups ● No significant meal related changes in ghrelin profile in RYGB, LASGB, or total gastrectomy groups ● Plasma ghrelin significantly inversely related to BMI (taking into account only obese subjects)

(continued)

Figure 2. Continued

Hormones measured	Limb length	Study groups	Time points	Measurements	Summary
Ghrelin, PYY, GLP-1 (49)	Not reported	Group 1: RYGB (n=8, 8 F); Group 2: GB (n=6, 6 F); Group 3: nonoperated weight matched to post-op RYGB and GB (n=8, 8 F)	Post-op only (RYGB: 9 to 48 mo post-op; GB: 25 to 85 mo post-op)	Overnight fast; oral U 13C-labeled glucose load (0.5 g/kg, 2% enriched with 13C glucose); Time 0=time immediately before glucose; blood samples collected at -120, -30, and 0 min and 15, 30, 45, 60, 90, and every 30 min	<ul style="list-style-type: none"> ● RYGB lost significantly more body weight than gastric band subjects ● No significant differences among 3 groups in terms of fasting ghrelin and GLP-1 ● Post-oral glucose load, ghrelin decreased in all groups and reached a nadir at 60 min ● Maximal postprandial suppression of ghrelin was significantly greater in RYGB than in other groups ● Fasting PYY significantly higher in RYGB group compared to other groups ● PYY response to oral glucose load significantly increased in RYGB group compared to other groups ● Significant exaggerated GLP-1 response to oral glucose load in RYGB group
Ghrelin (85)	Not reported	Group 1: post-RYGB (n=6, 3 F); Group 2: obese pre-RYGB (n=6, 1 F); Group 3: healthy obese, nonsurgical (n=6, 2 F); Group 4: lean (n=5, 4 F)	Group 1: 1.5±0.7 y post-op	Fasted blood samples collected and at 30-, 60- and 120-min post 75-g OGTT	<ul style="list-style-type: none"> ● Fasting serum ghrelin significantly lower in post-RYGB compared to lean controls and pre-RYGB groups ● Fasting serum ghrelin significantly higher in pre-RYGB group compared to obese nonsurgical group ● Fasting serum ghrelin significantly lower in obese nonsurgical group compared to lean controls ● Serum ghrelin during OGTT significantly lower in post-RYGB group compared to all other groups ● Serum ghrelin levels during OGTT significantly higher in pre-RYGB group compared to obese non-surgical group ● Serum ghrelin levels during OGTT significantly lower in obese nonsurgical compared to lean controls ● Magnitude of decline in serum ghrelin between 0 and 120 min post-OGTT was significantly smaller in all groups compared with lean controls
Double-blind, randomized controlled					
STUDY 3: PYY, GLP-1 (46)	STUDY 3: not reported	STUDY 3: Group 1: RYGB (n=7); Group 2: AGB (n=6); sex characteristics not reported	STUDY 3: 2 visits 9.5±1.5 (bypass) and 17±1.4 (banding) mo post-op	STUDY 3: subjects received either saline or somatostatin subcutaneously; blood collected at 60, 90, 120, 150, and 180 min; ad libitum meal at 60-min post-injection; to control rate of intake, 100-kcal of semi liquid meal was provided every 5 min until full	STUDY 3: <ul style="list-style-type: none"> ● Only RYGB subjects showed early and exaggerated responses of PYY and GLP-1 ● Significantly more energy consumed with somatostatin compared to saline ● Somatostatin inhibited release of gut hormone responses in both groups
^a BMI=body mass index. ^b GI=gastrointestinal. ^c VBG=vertical banded gastroplasty. ^d AGB=adjustable gastric banding. ^e BPD=biliopancreatic diversion. ^f EWL=excess weight loss. ^g LSG=laparoscopic sleeve gastrectomy. ^h PYY=peptide YY. ⁱ OGTT=oral glucose tolerance test. ^j AUC=area under the curve. ^k GLP-1=glucagon-like peptide-1.			^l HbA1c=hemoglobin A1c. ^m ARS=antireflux surgery. ⁿ GB=gastric band. ^o LAGB=laparoscopic adjustable banding. ^p ASGB=adjustable silicone gastric banding. ^q GBP=gastric bypass procedure. ^r NG=neuroglycopenia. ^s Ensure, Abbott Laboratories, Abbott Park, IL. ^t BND=gastric banding. ^u LASGB=laparoscopic-adjustable silicone gastric banding.		

Figure 2. Continued

When comparing RYGB to other surgical procedures, both of the reviewed studies found that GLP-1 levels were significantly higher in the RYGB subjects compared to those who underwent gastric banding (42,49). In these studies, the postoperative weight was not statistically different between groups, suggesting that weight change is not a primary regulator of GLP-1. Similarly, one study also compared the gastrointestinal hormone profile of RYGB subjects to that of a diet-induced weight loss group (44). Although the mean body weight was not significantly different between the groups, the peak GLP-1 level was significantly higher after RYGB compared to diet-induced weight loss (44). As previously mentioned, GLP-1 is secreted from the distal ileum in response to nutrient intake. Increased GLP-1 levels post-RYGB have been hypothesized to occur because of the surgical component that promotes a more rapid delivery of nutrients to the distal gut (51,52).

There were eight studies of more limited design that were reviewed (6,46,48-50,53-55) (Figure 2). As would be expected, a majority of the studies comparing pre- to post-RYGB levels found a significant increase in GLP-1 levels at post-RYGB compared to pre-RYGB (6,46,50,55). In contrast, two studies did not find any differences (53,54) and one study found that GLP-1 significantly decreased 2 years post-RYGB compared to pre-RYGB levels (48). The lack of consistent findings compared to the aforementioned studies may be explained by the fact that all three studies only sampled for GLP-1 in the fasted state (Figure 2) (48,53,54). GLP-1 is secreted in response to nutrient intake and perhaps these studies would have yielded different results had the study methodology included multiple sampling for gastrointestinal hormones pre- and post-meal consumption. The balance of data coming from well-designed studies that included controls and sampled for the gastrointestinal hormone at multiple time points indicated that GLP-1 significantly increases post-RYGB.

PYY Changes after RYGB

Of the strongest study designs that included control groups and/or multiple sampling points (45,47,49,56-59) (Figure 2), the general consensus is that postprandial PYY levels are higher in post-RYGB subjects compared to lean (45,56-58), normal weight (59), overweight (49, 58), obese (45,47,56,57), and/or individuals undergoing other bariatric procedures (45,49,58). More specifically, a majority of the aforementioned studies determined that the PYY response to a test meal or oral glucose tolerance test was exaggerated, occurred earlier, and remained elevated above baseline levels for the remainder of the sampling time period (45,47,49,56-58). One study evaluated total PYY and PYY₃₋₃₆ and found that both forms had the same postprandial response (58).

The remainder of the reviewed studies did not include multiple PYY sampling time points or a control group (6,46,48,60) (Figure 2). In the two studies that compared pre-RYGB to post-RYGB status, both found that post-RYGB PYY levels were higher compared to pre-RYGB (6,46). Findings from le Roux and colleagues (46) suggest that this change occurs as early as 2 days post-bypass, before any weight loss, and data from Borg and colleagues

(6) indicates that this effect can be seen as long as 6 months post-RYGB. In contrast, Karamanakos and colleagues (60) evaluated the gastrointestinal hormone response post-RYGB and post-laparoscopic sleeve gastrectomy and found that postprandial PYY significantly increased post-surgery; however, they did not statistically compare the PYY response between the two surgeries, and thus it is not known if there is a difference between the surgeries. In another study that did not use multiple sampling time points for gastrointestinal hormone analysis, but did have a control group (gastric banding subjects), fasting PYY increased in both groups, with no significant differences found between the two surgeries (48). PYY is released in response to a meal in proportion to the energy consumed, and perhaps different results would have been found had the authors sampled after food intake as well.

There is strong evidence that postprandial PYY levels increase post-RYGB and are higher compared to subjects who are lean, who have obesity, are overweight, and in subjects who have undergone other surgical procedures. Similar to GLP-1, the effect of RYGB on PYY levels can be seen as early as 2 days after surgery and the effect appears to be long term given that most of the studies reviewed here evaluated subjects months to years post-RYGB (6,45,46,48,49,56-60).

Leptin Changes after RYGB

More than half of the reviewed studies that measured leptin were of strong design (37,41,57,58,61-70) (Figure 2); however, some studies only compared pre-RYGB leptin levels to the post-RYGB state and did not make comparisons to the control group (eg, obese, lean) that was included in the study design (63,64,66). Similarly, others did not include a statistical analysis for leptin and only reported the values of the hormone pre- and/or post-RYGB (37,62) and, as a result, the leptin data from these two studies will not be discussed.

The leptin data are not as consistent as those reported for the gastrointestinal hormones. Some studies have demonstrated significantly lower fasting leptin concentrations in the post-RYGB patient population compared to pre-RYGB (67,68), normal weight (70), overweight (58), and obese (41,65,69) subjects, whereas others did not find a statistically significant difference between study populations (57,61,67). For example, Korner and colleagues (57) found similar leptin concentrations between lean and post-RYGB subjects that were significantly lower than the BMI-matched controls. This is an interesting finding, as the post-RYGB subjects were still considered to be overweight or have obesity and it would be expected that the lean individuals would have significantly lower leptin compared to both groups. Alternatively, Molina and colleagues (63) reported that leptin levels were significantly higher in a pre-RYGB compared to overweight subjects, most likely because their BMI was substantially higher than the overweight group (49 ± 6 vs 26.8 ± 2.2 , respectively) (63) and leptin is secreted in proportion to adipose mass. Molina and colleagues (63) did not evaluate post-RYGB leptin levels compared to the control group. Furthermore, of the studies reviewed, only two studies examined the correlation between anthropometric measurements (eg, BMI) and leptin levels (57,65). Stoeckli and colleagues (65)

determined that the change in leptin concentration was significantly correlated with change in BMI, with similar findings reported by Korner and colleagues (57). Due to control group variability, and differences in follow-up intervals, it is difficult to make definitive conclusions regarding the effect of RYGB on leptin concentrations.

Eleven additional studies that lacked a leptin control group were reviewed (6,54,63,64,66, 71-76) (Figure 2). In all of these studies, post-RYGB leptin concentrations were found to be significantly decreased compared to pre-RYGB (6,54,63,64,66,71-76). Furthermore, five of the studies conducted a correlation analysis between anthropometric measurements and leptin levels (63,66,71-73) with similar results reported between studies. Most determined that changes in weight (73), fat mass (73), and BMI (63,66) were significantly associated with changes in leptin post-RYGB. However, one study did not find a correlation between BMI and leptin concentrations after RYGB surgery (72), and another only evaluated preprocedure leptin concentrations with both baseline body weight and absolute weight reduction; no significant correlations were found between leptin and either variable (71). Taken together, the data strongly suggest that leptin decreases after RYGB and is associated with anthropometric measurements. These findings are congruent with the notion that leptin is secreted in proportion to body fat mass.

Ghrelin Changes after RYGB

A considerable amount of research has been devoted to ghrelin changes in RYGB patient populations and 25 studies were found that fit the previously described inclusion criteria (6,37,45,46,49,55-62,64-66,77-85) (Figure 2). Ghrelin was first described to be reduced in response to the RYGB procedure by Cummings and colleagues (37) in 2002. This finding was received with much curiosity because Cummings and colleagues (37) also found that ghrelin levels significantly increased after weight loss achieved by energy restriction, suggesting that the RYGB procedure had a positive effect on the “hunger hormone,” whereas other methods of weight loss did not. Because of that landmark study, studies of stronger design (37,45,46,49,56-58,64,77,79-82, 85) (Figure 2) have generally shown that the postprandial and/or fasted ghrelin concentration is significantly lower post-RYGB compared to pre-RYGB (64,82,85), lean (45,56,77,85), normal-weight (37,64,81), overweight (49,58), obese (37,56,79,81,85), and/or compared to other bariatric surgical procedures (49,58,81), with two studies not finding such an effect (46,57). Three studies also evaluated active ghrelin (57,58,80) and found significantly lower fasted ghrelin in post-RYGB subjects compared to those who have obesity (80) with similar postprandial findings in gastric banding (58) and in lean (57) subjects. The consistent finding of decreased ghrelin levels after RYGB procedure offers a partial explanation for the success of the procedure, since low ghrelin levels would not contribute to feelings of hunger. Decreased ghrelin occurs immediately post-op, as Lin and colleagues (82) evaluated subjects 30 minutes post-RYGB and found significantly decreased ghrelin levels compared to before RYGB. Studies indicate that this ghrelin effect is maintained for more than 1 year (37,45,49,56,58,77,79,81,85).

Researchers have also evaluated the fluctuations in the

postprandial ghrelin profile after RYGB by sampling at multiple time points after meal consumption. Similar secretion patterns have been reported across studies. For example, after RYGB it has been observed that the ghrelin profile is flat and does not have the meal-related fluctuations that have been observed in normal-weight individuals (37,81), those who have obesity (37,81), or subjects who underwent other types of weight loss surgeries (80). In addition, Cummings and colleagues (37) sampled for a 24-hour period and determined that the post-RYGB subjects did not have the same ghrelin diurnal rhythm found in normal weight individuals, those who have obesity, or in subjects who had lost weight by dietary restriction.

Although numerous studies have determined that ghrelin declines after RYGB more so compared to other surgical procedures (49,58,81), it is unclear what component of the surgery promotes this alteration. It has been suggested that because the distal stomach, the site of ghrelin release, is bypassed in the RYGB, ghrelin secretion is suppressed, thereby reducing hunger. To test the hypothesis that the RYGB procedure's success is primarily due to exclusion of the stomach and consequently ghrelin suppression, two studies have compared the RYGB procedure to that of other gastric surgeries that do not involve complete division of the stomach: gastrectomy and antireflux surgery (conducted in both lean and overweight subjects) (82). In terms of the gastrectomy, Lin and colleagues did not find a significant decrease in ghrelin levels post-gastrectomy like they had when comparing pre- to post-RYGB ghrelin levels (82). Similar results were evident in the antireflux surgery group; they did not see a significant decrease in ghrelin post-antireflux surgery in either the lean subjects or in subjects with obesity (82). Ghrelin levels in the post-antireflux surgery subjects were also significantly greater compared to those of post-RYGB subjects (82). This group was also interested in establishing what component of the RYGB procedure is responsible for the greatest decline in ghrelin levels (82). They collected plasma before surgery, 10 minutes after transecting the jejunum to form the Roux limb, 10 minutes after dividing the stomach to form the small gastric pouch, and immediately after completion of the surgery (82). As would be expected, they found that ghrelin levels significantly declined after dividing the stomach to form the small gastric pouch (82). Overall, authors (82) concluded that the RYGB's complete division of the stomach promotes the reduced ghrelin levels. In contrast, a second study evaluated another gastric surgery, a total gastrectomy, which also involves a complete division of the stomach (81). Compared to normal weight individuals, those with obesity, RYGB patients, and individuals who underwent gastric banding, those with a total gastrectomy had significantly lower ghrelin levels, further implicating the importance of the stomach for ghrelin release (81). This has clinical importance because weight loss surgeries that do not involve a bypass of the stomach may not sufficiently lower ghrelin levels to reduce hunger and promote weight loss and/or maintenance.

Eleven other studies were reviewed that were of weaker design (6,55,59-62,65,66,78,83, 84) (Figure 2). Some of the studies did compare ghrelin levels to a con-

trol group; however, they only sampled for ghrelin in the fasted state (61,62,65) and these studies will be discussed first. Similar to the stronger studies that included multiple sampling time points following meal consumption, ghrelin was found to be significantly lower in the post-RYGB group, compared to pre-RYGB (62), subjects who lost weight using conventional methods (62), and/or in those who underwent other weight loss surgeries (61,62). Alternatively, Stoeckli and colleagues (65) determined that ghrelin was lower in post-RYGB subjects compared to both individuals who have obesity and subjects who underwent gastric banding; however, it did not reach statistical significance. It is unclear whether the authors conducted a statistical test to compare the gastric banding subjects to that of RYGB because there was almost a 49% difference between post-gastric banding and post-RYGB ghrelin levels, but no statistics were reported regarding this difference (65). Overall, the data from these studies provides information regarding ghrelin changes post-RYGB compared to other subject groups; however, because these studies did not sample at multiple time points, it is impossible to determine the ghrelin secretion profile in response to a meal.

Studies that compared ghrelin levels between the pre- and post-RYGB state obtained unexpected results. For example, a majority of the reviewed studies did not find a difference in either fasted (6,60,83) or postprandial (83) ghrelin levels between pre- and 6 (6,78,83) to 12 months post-RYGB (60), whereas only two studies found that ghrelin increased during this same time period (66,84). Morinigo and others (59) also found that at 6 weeks post-RYGB fasted ghrelin levels had significantly decreased compared to pre-RYGB; however, at 52 weeks there was a significant increase in the hormone compared to the 6-week measurement and levels were comparable to that of baseline. It is unclear why the weaker studies did not find a significant decrease in ghrelin post-RYGB, as would be expected based on the data from the better designed studies discussed previously. Sample size may be an issue; Couce and colleagues (78) initially found a significant decline in ghrelin from pre- to both 2 hours and 10 days post-RYGB when the sample size was 49 and 18, respectively. However, at 6 months post-op, the study sample had decreased to 11 and the finding was no longer statistically significant (78). However, this cannot be the primary reason for inconsistent results because with the exception of Borg and colleagues (6), who did not report attrition, the remainder of the studies reported 100% follow-up rates from pre- to post-RYGB. An alternative explanation is that perhaps the shorter follow-up time (≤ 1 year) failed to capture the true time course given that a majority of the stronger studies evaluated subjects for years post-RYGB.

Overall, data from the stronger studies indicates that ghrelin is greatly reduced in the post-RYGB state compared to those who are lean, normal weight, overweight, or have obesity, or who have had other weight loss surgeries. The mechanism by which this occurs is likely related to the surgical component of the RYGB that bypasses the stomach, from which ghrelin is primarily secreted. Data from the weaker studies are not as conclusive, with some studies finding no change from pre- to post-RYGB and others actually reporting an increase.

Differing methodologies might partially explain this discrepancy.

SYNTHESIS AND TRANSLATION

RYGB is an effective weight loss treatment option for those in which traditional therapies have failed. It offers long-term weight loss that may be the result of the physiological and gastrointestinal hormone changes associated with the procedure. This review looked at the current evidence showing that alterations in GLP-1, PYY, leptin, and ghrelin do occur postoperatively and generally do so in a favorable direction. In the majority of studies, post-RYGB GLP-1 and PYY concentrations were usually found to be higher, whereas ghrelin levels were typically lower compared to the concentrations of these hormones in individuals undergoing other surgical procedures, individuals who were normal and overweight, and those who lost weight by diet alone.

There are notable gaps in the literature. For instance, several of the reviewed studies did not include an appropriate control group and only evaluated changes pre- and post-RYGB. Therefore, it is not always easy to ascertain whether it was a component of the RYGB that caused the improvement in gastrointestinal hormones. Although it would be best to have a double-blind, randomized control study design, in studies involving RYGB and other surgical procedures this is not always possible due to logistical and ethical issues. In addition, follow-up times varied substantially between studies, and in some studies only one time point was measured (ie, cross-sectional studies); therefore, it was difficult to make comparisons between studies. Moreover, some of the reviewed studies only included one sampling time point for gastrointestinal hormones, usually in the fasted state. It is of interest to determine how these appetitive hormones are affected in the postprandial state. Therefore, future studies should sample before and after a meal to capture the gastrointestinal hormone response profile. Furthermore, studies that vary the macronutrient composition need to be performed to shed light on how gastrointestinal hormones contribute to satiety in post-RYGB patients, since secretion of gut hormones is often related to protein, carbohydrate, or fat ingestion. Future research in these areas is warranted.

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