

Review article

Does ghrelin really matter after bariatric surgery?

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Ghrelin is a potent orexigenic (appetite-stimulating) peptide secreted by the X/A-like cells of the stomach that circulates in the blood in measurable levels [1–3] and signals the brain's pathways of energy balance [4–9]. The 24-hour variation in serum ghrelin, with an increase before meals and suppression after food intake, suggests a role in meal-to-meal regulation [2,10–12]. When administered to rodents or humans, ghrelin acutely stimulates food intake, and its chronic administration increases body weight [1,2]. It has been suggested that ghrelin participates in the adaptive response to weight loss surgery [6,13–15]. Differences in fasting plasma ghrelin levels have been found among patients who have undergone laparoscopic Roux-en-Y gastric bypass (LRYGB), laparoscopic adjustable gastric banding (LAGB), and biliopancreatic diversion (BPD), and between patients who underwent the same surgical procedure (Table 1). However, as detailed in this review, the studies are difficult to compare because the patients studied have been in different states of energy balance, the technique of sampling and the ghrelin assays were different, and either the fasting or postprandial ghrelin levels have been reported.

Two questions remain to be answered. First, what are the mechanisms underlying the changes in ghrelin secretion after weight loss surgery? It is possible that the various surgical procedures that modify gastric anatomy and innervation have a different impact on ghrelin levels in response to food intake and nutritional status. Second, could the changes in circulating ghrelin levels after bariatric surgery

partly account for the weight loss and the long-term success of the surgery? This review summarizes recent knowledge on serum ghrelin level in patients undergoing the LRYGB, LAGB, and BPD procedures. The possible mechanisms by which ghrelin could potentiate and maintain weight loss after bariatric surgery are discussed. We performed a systematic literature review (96 articles) of PubMed citations using the following key words: ghrelin, bariatric surgery, gastric bypass, LAGB, biliopancreatic diversion, gastrectomy, and weight loss.

After any of the three bariatric surgical procedures, patients usually lose between 47% and 70% of excess body weight in 2 years, although the long-term weight loss varies [16]. The changes in gastric anatomy and physiology resulting from these three procedures could result in variations in the circulating ghrelin levels. Postoperatively, ghrelin levels depend on the functional integrity of the remaining fundus, the size of the gastric pouch [17,18], the length of the Roux limb or biliopancreatic limb [7,19], and/or the adaptive responses of body weight homeostasis [6,13–15]. Knowledge of the role of ghrelin in bariatric surgery might lead to a better understanding of one of the major determinants of human energy homeostasis and might also lead to the development of more effective bariatric procedures in the future.

Physiology of ghrelin

Ghrelin, the peptide hormone secreted by gastric endocrine cells [20], has attracted much interest for its dual effects. Ghrelin, the endogenous ligand for the growth hormone secretagogue receptor [21], regulates growth hormone (GH) release [22], and plays a role in the regulation of food intake and energy balance. When administered either cen-

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Table 1
Bariatric surgery (LRYGB, LAGB, BPD) and ghrelin studies

Authors	Study design	Surgery type/no.	Follow-up (mo)	BW change	Fasting total ghrelin level (pmol/L)	RIA method	Post-test meal suppression
Holdstock et al. [7] 2003	Longitudinal	LRYGB/66	12	−29.8 kg	141 ± 70 (↑)	Phoenix	NA
Faraj et al. [46] 2003	Longitudinal	LRYGB/25	Weight stable,* 17 ± 4.9	−35.9 ± 10.0%	54.2 ± 15.8 (no change)	Phoenix	NA
		LRYGB/25	Weight reducing,† 12.3 ± 5.7	−37.0 ± 9.3%	80.8 ± 27.7 (↑)	Phoenix	NA
Stoekli [58] 2004	Longitudinal	LRYGB/5	24	−29.5 ± 5.5 kg	408.0 ± 147.8 (↑, <i>P</i> > .05)	Phoenix	NA
Vendrell [64] 2004	Cross-sectional	(Open) RYGB/34	6	−14.7 kg/m ²	1.8 ng/mL (↑)	Linco	NA
Cummings [13] 2002	Cross-sectional	LRYGB/5	16.8 ± 4.8	−36%	905 ± 213 (↓)	Phoenix	Suppressed
Lin [60] 2004	Cross-sectional	LRYGB/34	30 min postoperatively	NA	246 ± 13 (↓)	Phoenix	NA
Leonetti [15] 2003	Cross-sectional	LRYGB/11	12	−10.72 kg/m ²	213.5 ± 73.9 (↓)	Phoenix	Suppressed
Tritos [54] 2003	Cross-sectional	LRYGB/6	18 ± 8.4	−27.7 kg	69 (↓)	Phoenix	Suppressed during OGGT
Morínigo [61] 2004	Cross-sectional	LRYGB/8	1.2	−10.3% ± 1.5%	844.1 ± 58.2 (↓)	Linco	Suppressed
Geloneze [55] 2003	Longitudinal	(Open) RYGB/14	12	Preoperative nondiabetic group; −8.1%	213 ± 67 (↓)	Phoenix	NA
		(Open) RYGB/14	12	Preoperative type 2 DM group; −6.8%	240 ± 23 (↓)	Phoenix	NA
Fruhbeck [62] 2004	Cross-sectional	LRYGB/6	6.1 ± 0.4	−50%.1 ± 4.4%	117 ± 34 (↓)	Linco	NA
Korner [47] 2005	Longitudinal	LRYGB/12	35 ± 5	−36 ± 2.9%	425 ± 54 (no change/Active octanoylated ghrelin 143 ± 27 (↓))	Phoenix/Linco	Suppressed/Suppressed
Christou [63] 2005	Cross-sectional	(Open) RYGB/26	36	Successful weight loss group; −72%	312 ± 35 (↓)	Phoenix	NA
		(Open) RYGB/16	36	Unsuccessful weight loss group; −29%	238 ± 25 (↓)	Phoenix	NA
Stoekli [58] 2004	Longitudinal	LAGB/8	24	−22.8 ± 2.9 kg	838.9 ± 387.3 (↑)	Phoenix	NA
Fruhbeck [18] 2004	Cross-sectional	LAGB/7	7.0 ± 0.6	−42.2% ± −3.1%	480 ± 78 (↑)	Linco	NA
Dixon [67] 2005	Longitudinal	LAGB/17	26	−28.0%	(↑)	Linco	NA
Schindler [69] 2004	Cross-sectional	LAGB/23	6	−15.7 ± 1.4 kg	127.2 ± 13.2 (↑)	Peninsula	NA
Hanusch-Enserer [68] 2004	Longitudinal	LAGB/18	12	−31.5 kg	261 ± 72 (↑)	Phoenix	NA
Nijhuis [70] 2004	Longitudinal	LAGB/7	12	−33.2 ± 5.8 kg/m ²	904 ± 127 (↑)	Phoenix	NA
Leonetti [15] 2003	Cross-sectional	LAGB/10	12	−6.06 kg/m ²	314.2 ± 84.3 (↓)	Phoenix	Suppressed
Fruhbeck [18] 2004	Cross-sectional	BPD/3	4.4 ± 0.8	−54.2 ± 4.3	406 ± 86 (↑)	Linco	NA
Adami [73,90] 2004	Longitudinal	BPD/24	12	−39.6 kg	310.8 ± 47.7 (↑)	Phoenix	NA
		BPD/6	2	−19.4 kg	210.2 ± 120.7 (NS)	Phoenix	NA

Data in kilograms or percentages refers to estimated weight loss. Data in kilograms per meter squared refers to body mass index. LRYGB = laparoscopic Roux-en-Y gastric bypass; LAGB = laparoscopic adjustable gastric banding; BPD = biliopancreatic diversion; BW = body weight; NA = not available; DM = diabetes mellitus; NS = not significant.

* Neutral energy balance.

† Negative energy balance.

trally or peripherally to rodents, ghrelin increases food intake and body weight [23,24]. Its effects on food intake are mediated by way of the NPY/Agouti gene-related protein neurons in the hypothalamic arcuate nucleus [25].

The stomach is a major source of circulating ghrelin [1,2]. The gastric fundus contains 10–20 times more ghrelin per 1 g of tissue than the duodenum, which is the next richest source [1,20]. Lesser concentrations of ghrelin are present in the jejunum and ileum, generally diminishing with increasing distance from the stomach [1,2,10]. Gastric ghrelin-producing cells reside in the oxyntic glands, in contact with the basolateral membrane adjacent to the bloodstream, and most do not have direct contact with the stomach lumen [1,26]. Minor amounts of ghrelin are produced in diverse additional tissues, often detectable only by reverse transcriptase-polymerase chain reaction [27]. These sites include the lungs, pancreatic islets, gonads, adrenal cortex, placenta, and kidney, among others [28]. The main effects of ghrelin are GH release and stimulation of food intake by activation of ghrelin receptors in the hypothalamus/pituitary area [29]. Ghrelin receptors are also present in peripheral tissues, such as the pancreas, heart, testis, ovaries, and adipose tissue, to name a few [27,30,31]. All these peripheral tissues/organs are potential targets of ghrelin action, although less well defined. The circulating concentration of ghrelin is determined by many physiologic factors. The first is body weight. Plasma ghrelin concentrations correlate negatively with body mass index (BMI) over a wide range [13,23]. Ghrelin secretion is upregulated under conditions of negative energy balance and downregulated in the setting of positive energy balance [7–9]. In the presence of a negative energy balance, such as low-calorie diets [13,32], chronic exercise [9,33], cancer anorexia [32], chronic obstructive pulmonary disease [34], and anorexia nervosa [9], the serum ghrelin concentrations are increased. Decreased ghrelin was found in subjects who gained weight through overfeeding and in anorexia nervosa patients during weight recovery [35]. In human obesity, the ghrelin concentration is low, which may be related to the high caloric intake. Obese individuals, after a 5% diet-induced weight loss, manifest significantly increased circulating ghrelin levels [36]. In contrast to what subjects with simple or common obesity, who have lower circulating ghrelin levels than lean controls, individuals with Prader-Willi syndrome, the most common form of genetic obesity, have very high levels of ghrelin [37]. Because these patients tend to have a voracious appetite, much research has been done to try to understand the mechanism of underlying elevated ghrelin levels in Prader-Willi syndrome [38].

In addition to the long-term effect of energy balance on ghrelin levels, ghrelin levels are also regulated acutely by food intake and demonstrate a meal-to-meal variation. Plasma ghrelin levels decrease shortly after food ingestion, a response that may involve an increase in circulating insulin and glucose levels [36,39] and/or the contact of nutrients

with the gastrointestinal lumen [40]. However, insulin is not the only factor responsible for postprandial suppression of ghrelin [41], and other factors are likely to be involved [42]. The diurnal variation of ghrelin secretion in normal subjects appears to be entrained to the times of the meals taken [10]. The temporal pattern of plasma ghrelin concentration consists of a rise just before the onset of meals and a postprandial decline during the daytime. The physiologic signals that initiate eating in humans are poorly understood. A preprandial rise in plasma ghrelin concentration suggests that ghrelin may be a candidate for a meal-initiation signal [2,10–12]. Thus, ghrelin could play a role in premeal hunger and meal initiation, acting as an orexigenic counterpart to the numerous meal-related satiation factors such as cholecystokinin, peptide-YY (PYY), glucagon-like peptide 1. These satiating gut hormones rise rapidly postprandially [4], and the level of circulating ghrelin simultaneously begins to decrease. The mechanisms underlying postprandial ghrelin suppression are unknown. Although the stomach produces the most ghrelin, it has been shown that neither gastric nutrients nor gastric distension affect ghrelin levels [42].

Together, these findings suggest that circulating ghrelin levels fluctuate in response to changes in body weight, as well as acutely in response to meals. This is consistent with the role of ghrelin in its adaptive response to changes in body weight and perhaps in long-term energy homeostasis [43].

Ghrelin and bariatric surgery

As a result of bariatric surgery, energy intake is markedly decreased; patients experience decreased hunger, early fullness, and enhanced satiety. Moreover, the ingested food bypasses important parts of the digestive system, because of the increased food transit time, resulting in partial malabsorption [44,45]. Bariatric operations can be classified into restrictive, malabsorptive, and mixed techniques. The placement of an adjustable gastric band represents a purely restrictive procedure, producing a small gastric pouch and a narrow passage into the remainder of the stomach (Fig. 1b). Gastric bypass represents a mixed technique [45] that combines the restriction derived from leaving a small stomach pouch near the esophagogastric junction, excluding the greater curvature, together with a small malabsorptive component derived from bypassing most of the stomach and duodenum (Fig. 1a). Previous studies have addressed the impact of the type of bariatric surgery on fasting ghrelin concentrations and related it to weight loss. Differences in the fasting total plasma ghrelin levels among patients who have undergone LRYGB, LAGB, and BPD have been found, with differences even in patients who underwent the same procedure [7,15,46]. Table 1 outlines the various studies on serum ghrelin variations among patients who have undergone LRYGB, LAGB, and BPD. Most studies have reported total plasma ghrelin concentrations. Only one

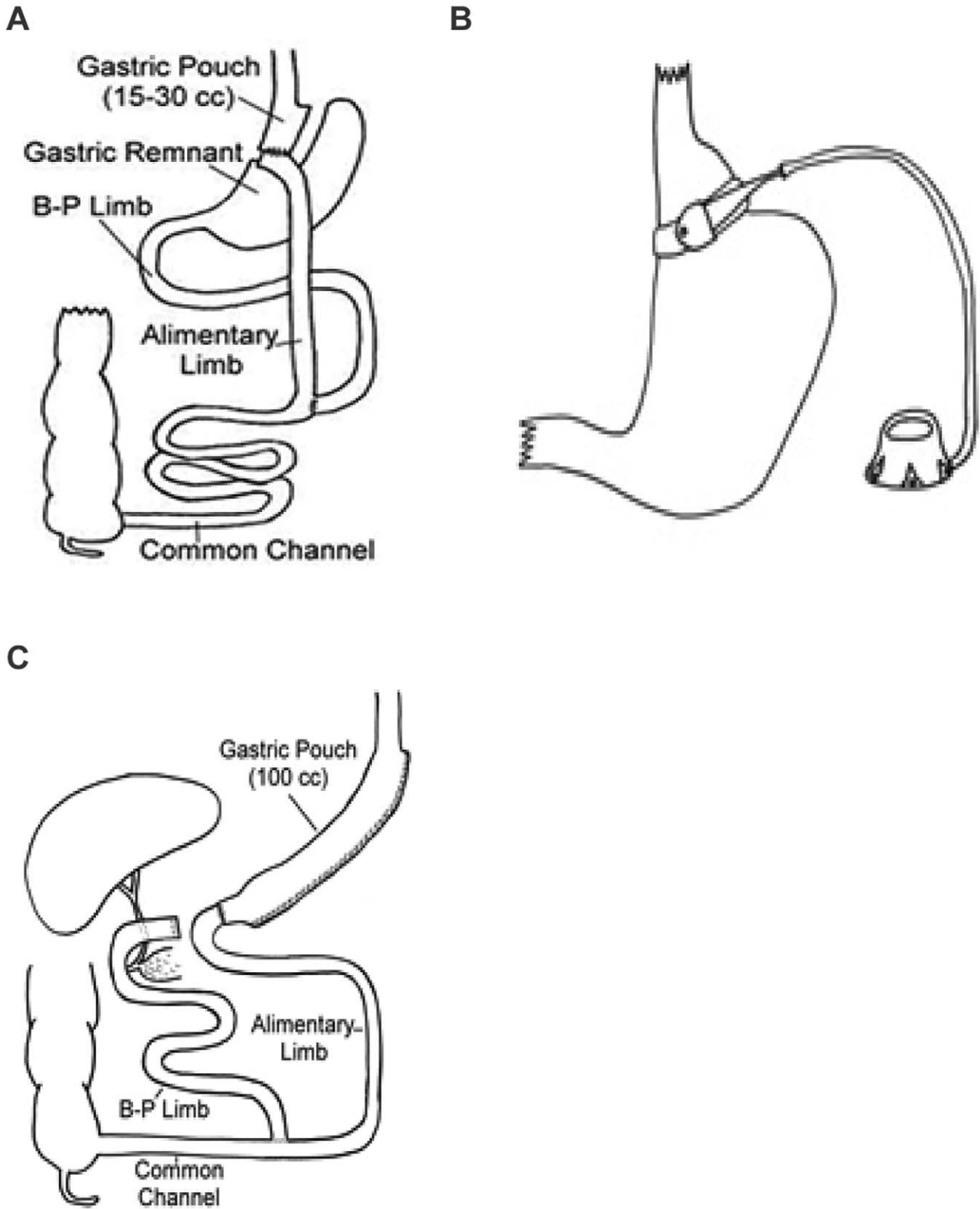


Fig. 1. (A) LRYGB, (B) LAGB, and (C) BPD.

study has reported on the active ghrelin levels [47]. Acylated ghrelin is the active form of ghrelin and is very unstable at room temperature. The best technique of sampling is to collect it in chilled ethylenediaminetetraacetic acid tubes, centrifuge within 30 minutes of collection, and acidify the serum, avoiding multiple freezing and thawing procedures [48]. Of all the studies we report on here, only one used acidification of samples [47].

LRYGB and ghrelin

LRYGB is the most effective and commonly accepted method to achieve major weight loss and is the treatment of choice for persons with morbid obesity [49–51]. LRYGB can be performed safely and effectively in super-super obese patients (BMI ≥ 60 kg/m²) [52]. LRYGB leads approximately to a 40% loss of body weight that is preserved over the long term compared with the weight loss after the LAGB procedure [14,45].

Ghrelin levels are inversely related to body weight, and obese individuals display low ghrelin levels [23]. Diet-induced weight loss has been shown to increase ghrelin levels [13,53], implying that ghrelin may play a role in countering such weight loss by increasing appetite and energy intake. Because ghrelin levels have been shown to be low after LRYGB in some studies [13,15,47,54–59], it has been proposed that lower ghrelin levels may contribute to the success of some surgical weight loss procedures, including LRYGB [13,46,55] and possibly LAGB [15]. However, data have been inconsistent [6,7,46,60–62]. Cummings et al. [13,14], in a cross-sectional study, was the first to report low total plasma ghrelin concentrations in 5 obese patients 9–31 months after LRYGB, who were still obese, compared with those in a group of matched obese controls [13,14]. The investigators hypothesized that the small size of the residual gastric pouch and the stoma between it and the jejunum might be responsible for the early satiety and limited the amount of food consumed. Furthermore, in the study by Cummings et al. [13,14], the subjects who underwent LRYGB displayed none of the meal-related oscillations found in lean and obese controls. Their hypotheses was that although an empty stomach is associated with an increased ghrelin level in the short term, it is possible that the permanent absence of food in the stomach and duodenum that results from gastric bypass causes a continuous stimulatory signal that ultimately suppresses ghrelin production. This could explain why a continuously empty stomach and duodenum would become depleted of ghrelin after prolonged fasting, leading to a decrease in fasting plasma ghrelin levels. These findings suggest that ghrelin suppression may be one mechanism by which LRYGB reduces hunger and causes long-term weight loss. The investigators also hypothesized that the gastric pouch, not completely excluding the gastric fundus, or a short biliopancreatic limb, would allow contact of nutrients with the

main sites of ghrelin secretion. Under these conditions, the secretion of ghrelin could partially retain its dynamics after bariatric surgery.

The effect of the Roux limb length on weight loss and ghrelin level after LRYGB is controversial. In the prospective study by Choban and Flancbaum [19], a longer Roux limb compared with the standard length (100-cm-length Roux limb) effectively increased excess weight loss in superobese patients after LRYGB. They did not evaluate the serum ghrelin levels in their study. The increased weight loss could have been a result of the effect of different limb lengths on ghrelin level after LRYGB [19,51]. Therefore, differences in surgical technique could play a role in the varying results of ghrelin levels after surgery.

Similar to the results of Cummings et al., Geloneze et al. [55] reported, in a longitudinal study, that the total plasma ghrelin levels had significantly decreased 1 year after LRYGB. Lin et al. [56] had subsequently observed that circulating ghrelin levels decline as early as 30 minutes after LRYGB, a change not observed with other gastric procedures (vertical banded gastroplasty [63] and antireflux surgical procedures). Morínigo et al. measured the total plasma ghrelin levels in response to a standardized test meal in obese patients before and 6 weeks after LRYGB [57]. The fasting serum total ghrelin levels were decreased 6 weeks after surgery but were not suppressed after the test meal. They concluded that the adaptive response of ghrelin to weight loss was already impaired 6 weeks after LRYGB. Fruhbeck et al. [18,62] found that the fasting total ghrelin levels failed to increase during substantial weight loss 6 months after LRYGB but did increase in response to lesser weight loss 7 months after LAGB and 4 months after BPD. Christou et al. [59] reported that the fasting ghrelin level was significantly lower in patients at 36 months after open RYGB compared with lean controls, regardless of the amount of weight loss. They concluded that the amount of weight loss after RYGB did not correlate with the pre- or postprandial plasma ghrelin levels. In a cross-sectional study, Korner et al. [47] measured both total and active octanoylated ghrelin in the fasting state and in response to a liquid test meal in lean patients, weight-stable patients after RYGB, and obese nonoperated subjects. The fasting plasma total and octanoylated ghrelin levels were similar in the RYGB and BMI- and age-matched controls but were greatest in the lean controls. The response to the test meal was comparable between the lean and RYGB groups, and the magnitude of suppression was significantly diminished in the BMI- and age-matched controls compared with the lean group. The magnitude of the maximal postmeal suppression of active ghrelin was more marked than with total ghrelin. They concluded that, in RYGB, the absence of the compensatory increase in ghrelin that usually occurs with diet-induced weight

loss may contribute to weight loss and the ability of an individual to maintain their weight loss after RYGB.

In contrast to previous data, Holdstock et al. [7], in a prospective study of 66 patients, reported increased ghrelin levels 6 months after LRYGB compared with the preoperative levels. The fasting ghrelin concentrations at 12 months after LRYGB were similar to those of obese, nonoperated control subjects. A subgroup of 10 patients demonstrated ghrelin levels 12 months after surgery that were similar to those of 10 BMI-matched women before surgery. The investigators postulated that it is the lowered caloric intake rather than LRYGB that affects ghrelin levels.

All the studies of patients who underwent LRYGB showed a massive decrease in BMI. One would expect the massive decrease in BMI achieved with LRYGB to trigger an elevation in ghrelin levels. Of the 13 studies of patients who underwent LRYGB, 4 [7,46,62,64] showed an increase in ghrelin levels after surgery and 9 showed a paradoxical reduction in plasma ghrelin levels (Table 1). It is possible that these different outcomes depend on how and when the postoperative samples were taken (i.e., whether subjects were actively losing weight or had achieved a stable, lower BMI), as well as the differences in surgical techniques across centers. A recent longitudinal study did not show changes in fasting ghrelin levels after RYGB [65]. Examining the totality of the cross-sectional and prospective studies with varying follow-up intervals (≤ 36 months) and a wide range of BMI reduction, no evidence was found of a consistent suppression of circulating ghrelin (Table 1). Thus, it is difficult to reconcile the existing data and formulate a conclusion as to the effect of LRYGB on ghrelin release.

More importantly, to our knowledge, no study to date has demonstrated that ghrelin levels postoperatively are predictors of success in patients after LRYGB [59]. Fruhbeck et al. [58] also reported that LRYGB and total gastrectomy patients showed similar ghrelin concentrations, although significant differences in BMI between the two groups 6 months after surgery. The investigators concluded that the reduction in circulating ghrelin concentrations in LRYGB patients 6 months after surgery is not determined by active weight loss but rather depends on the surgically induced bypass of the ghrelin-producing cell population of the fundus [58].

LAGB and ghrelin

LAGB, a purely restrictive bariatric procedure, involves the placement of a prosthetic band around the upper stomach to partition it into a small, proximal pouch (30 cm³) and a large, distal remnant, connected through a narrow constriction (Fig. 1b). The band aperture can be adjusted non-invasively, as needed. This leads to an average weight reduction from baseline of 28%, with a maximal effect seen ≤ 2 years after surgery [66]. In most studies, patients who

had undergone LAGB had greater ghrelin levels, in proportion with their weight loss. Dixon et al. [67] hypothesized that the restricted proximal stomach pouch present during optimal LAGB adjustment induced satiety by altering the neural and hormonal messages arising from the area. They also found that optimal LAGB restriction would increase both fasting and postprandial feelings of satiety, allowing weight loss and preventing weight regain. Plasma ghrelin levels appeared unrelated to the LAGB satiety effect. A study recently published by Stoeckli et al. [62] of patients after LRYGB and LAGB showed that the plasma ghrelin levels were significantly increased in the LAGB group. They suggested the plasma ghrelin response after weight loss is impaired after exclusion of major parts of the stomach and duodenum (LRYGB) and the smaller long-term weight loss after LAGB compared with LRYGB may result, at least in part, from an absence of increases in plasma ghrelin levels after LRYGB [62]. Hanusch-Enserer et al. [68] reported that obese patients presented with unchanged fasting ghrelin concentrations during the first 6 months that had increased at 12 months after LAGB. The investigators suggested that gastric restriction by LAGB would prevent the early adaptive increase in ghrelin secretion, which would counteract further weight reduction using dietary protocols. Fruhbeck et al. [18] found that the total ghrelin concentrations were approximately four times greater in patients who had undergone LAGB than in subjects who had undergone LRYGB. Schindler et al. [69] showed that fasting total plasma ghrelin levels had increased 6 months after LAGB, inducing early satiety and inhibiting eating to a greater extent than that usually seen after diet-induced weight loss alone. The increase of ghrelin correlated significantly with the extent of weight loss [53,69]. Nijhuis et al. [70] demonstrated that fasting plasma ghrelin levels increased 2 years after LAGB. In the cross-sectional study by Leonetti et al. [15], patients who had undergone LAGB had greater fasting total ghrelin levels than patients who had undergone LRYGB. Both groups of patients also had lower ghrelin levels than normal-weight subjects and BMI-matched obese patients. The ghrelin profile in the two groups who had undergone LRYGB and LAGB did not show any meal-related changes, in contrast to what was observed in the BMI-matched obese and normal-weight control groups.

In conclusion, most studies have reported that ghrelin levels increase after LAGB. LAGB might influence ghrelin levels differently, because it preserves the stomach in its anatomic site and does not exclude the major ghrelin-producing tissues in the gastric fundus from contact with food. Thus, similar to diet-induced weight loss, ghrelin levels increased after LAGB in response to the energy restriction. Despite the increase ghrelin levels, appetite is reduced and the sensation of fullness increased, with weight loss sustained over time with the appropriate tightness of the band.

BPD and ghrelin

BPD is a restrictive and malabsorptive operation that consists of a sleeve gastrectomy, including an extended gastrectomy, leaving only a 200–400-cm³ fundus [71], with a very long Roux-en-Y reconstruction at 50 cm from the ileocecal valve (Fig. 1c). Malabsorption occurs because the pancreatic and biliary secretions are diverted to the distal 50 cm of the ileum. Thus, most of the small intestine contains either digestive juices without food or food without digestive juices, and absorption is limited to the terminal ileum in which these two are briefly combined in a common channel. The reduction of circulating ghrelin levels might be a consequence of the loss of gastric cell mass because of the changes in gastrointestinal anatomy resulting from the surgical procedure. Nadreau et al. [72] showed that a decrease in digestible energy and food intake led to significant weight loss in BPD-operated rats. BPD can cause significant complications, including protein malnutrition, hypocalcemia and metabolic bone disease, foul-smelling diarrhea, and iron, vitamin B₁₂, and fat-soluble vitamin deficiencies [50]. Most American surgeons are reluctant to perform this operation, and it is generally reserved for the super-obese (BMI >50 kg/m²). Adami et al. [73] observed an initial reduction (5 days postoperatively) in fasting ghrelin concentrations after BPD, followed by a significant increase in the fasting serum ghrelin level at 12 months. After extended removal of the distal stomach, both the remnant gastric fundus and the extragastric ghrelin-producing structures can compensate well and return the circulating ghrelin levels to baseline [8,20,74].

Total gastrectomy and ghrelin

Rodent studies have demonstrated a reduced circulating ghrelin level 10 weeks after gastric surgery that was proportional to the amount of fundus resected, suggesting that extragastric sources of ghrelin amount to no >20% of the hormone in circulation [75,76]. Gastrectomy in humans has been associated with an immediate (<30 minutes) decline in ghrelin levels [2]. Long-term gastrectomies have been shown to chronically decrease circulating ghrelin levels. Patients who have undergone total gastrectomy have circulating ghrelin concentrations reduced by 55% compared with the control group [77]. It has been demonstrated that most circulating ghrelin originates from the stomach, with a smaller portion from the small intestine. Leonetti et al. [15] reported that patients who had undergone total gastrectomy had fasting plasma ghrelin levels much lower than those of the controls, LAGB, and LRYGB groups and also did not show significant physiologic oscillation in relation to food.

Roles of vagus nerve in ghrelin secretion

The contribution of vagal nerve activity to the secretion of ghrelin has been studied in experimental animals [1,78].

The presence of ghrelin receptors on the vagal nerve and the transport of ghrelin receptors through the vagal neurons to the periphery has been confirmed [79,80]. Although vagotomy results in a reduction of food intake, the meal-dependent response of ghrelin was not affected in rats [12]. Truncal vagotomy increases plasma ghrelin levels, indicating that the vagus nerve exerts an inhibitory influence over ghrelin secretion [81,82]. This finding agrees with the increase in ghrelin secretion observed during a fasted condition, a time in which vagal (i.e., parasympathetic) activity is at a nadir. Recently, le Roux et al. [78] determined whether humans with truncal vagotomy are sensitive to ghrelin. They found that patients with a history of gastric or esophageal surgery and transection of the anterior and posterior truncal vagus nerve frequently have a loss of appetite and weight loss. They found that ghrelin did not stimulate food intake in patients with surgical procedures involving vagotomy. Their data have indicated that an intact vagus nerve is required for exogenous ghrelin to increase appetite and food intake in humans [78]. Data on vagal innervation after gastric bypass are controversial. Some studies have indicated that vagal innervation in the excluded stomach could be preserved after gastric bypass, although others have not [83,84]. In the LRYGB procedure, dividing the lesser omentum and making a small upper gastric pouch intentionally transects the nerve of Latarjet [85,86]. Ghrelin seems to act differently from other hormones secreted by the stomach. The cholecystokinin, serotonin, and vasoactive intestinal peptide responses to meals were not altered by gastric bypass [87,88], and its secretion could be modified by the altered gastrointestinal anatomy.

It has also been reported that LRYGB induces early hormonal changes (insulin, insulin-like growth factor-1, leptin, adrenocorticotrophic hormone) preceding significant changes in BMI [89], suggesting that this procedure results in endocrine changes, perhaps independently of BMI. Therefore, one can hypothesize that intentionally or inadvertently cutting the vagal branches during LRYGB would affect circulating ghrelin levels, decrease appetite, and lower energy intake, resulting in long-term weight loss.

Ghrelin level and energy balance

Holdstock et al. [7] compared the fasting ghrelin levels in 10 nonoperated and 10 operated obese, BMI-matched women. LRYGB resulted in a 22% and 30% weight loss at 6 and 12 months, respectively. The ghrelin levels increased significantly by 44% and 62%. No evidence was found that LRYGB surgery had an effect on ghrelin levels, independent of weight loss [7]. They observed that circulating ghrelin levels in LRYGB patients continued to be primarily produced by the disconnected stomach and the control of the ghrelin-producing endocrine cells is unaltered. These changes were all related to changes in BMI and reflect the new state of energy balance achieved. They concluded that

it was not LRYGB surgery per se, but the lesser caloric intake that directly affected the ghrelin levels. Faraj et al. [46] reported that the effect of LRYGB on circulating ghrelin levels depends on the energy balance status at the time of the study. Subjects who had achieved a stable postoperative weight (neutral energy balance 17.5 ± 4.9 months postoperatively) had fasting ghrelin levels similar to their preoperative values. The ghrelin levels in subjects who were still actively losing weight (negative energy balance 12.3 ± 5.7 months postoperatively) were increased, similar to that observed after other modes of weight loss [7,33]. The fasting plasma ghrelin concentrations after surgery in nearly all subjects, whether weight stable or weight reducing, have been lower than the levels reported in either normal-weight or matched obese subjects. The investigators hypothesized that low circulating levels of this orexigenic hormone could contribute to initial weight loss and/or maintenance of weight loss after this type of gastric bypass surgery [16]. The postoperative increase in ghrelin in weight-reducing subjects suggests that ghrelin-secreting cells can increase the production of ghrelin in response to a negative energy balance, even if the gastric fundus and upper small intestine are not exposed to incoming nutrients. They suggested that postoperative serum ghrelin might be dependent on the weight loss status. Consequently, it appears that energy balance, but not body weight per se, may be the critical determinant of circulating ghrelin levels after LRYGB. The disparate results in the published data imply that the mechanisms by which LRYGB induces weight loss engage complex interactions between the mechanical effects of the surgery and the neuroendocrine responses involved in energy homeostasis. In the extended study by Adami et al [90], a slow increase of serum ghrelin was observed at 2 months after BPD with increasing levels at 12 months. A rise in the serum ghrelin concentration could correspond to a decrease in body weight. Food intake and serum ghrelin concentration had no clear relationship after gastrointestinal surgery for obesity. The gradual postoperative increase in serum ghrelin concentration could reflect changes in body weight and body fat mass and, therefore, corresponding to the achievement of a new state of energy balance.

Although the focus of this review was ghrelin, many other gut peptides change after bariatric surgery, particularly after gastric bypass surgery. Of interest are the changes observed with PYY and glucagon-like peptide 1 levels, likely candidates in the increased long-term satiety observed after bariatric surgery [63,91]. The changes in incretins after bariatric surgery was the object of a recent review [92]. The changes in PYY after bariatric surgery have also been shown in many studies [47,91,93]. Because the system regulating food intake and energy homeostasis is extremely complex, it is expected that more than one peptide candidate will be responsible for appetite control after bariatric surgery [47,92,94].

Conclusion

All current bariatric surgeries result in weight loss of large magnitude, correction of co-morbidities and excellent short-term and long-term outcomes [16,95,96]. Together with the spectacular weight loss seen in bariatric surgery, endocrine changes take place, particularly after LRYGB. Favorable changes in incretins and PYY levels after LRYGB have been demonstrated. Because ghrelin seems to play a key role in the complicated energy balance loop, it is logical to hypothesize that its changes after surgery could affect the success of the surgery. The literature review has clearly shown a robust increase of ghrelin after LAGB in proportion to the weight loss. The changes in ghrelin levels after LRYGB are less consistent, at times reported to be paradoxically low or not rising in proportion to the weight loss. However, well-controlled prospective studies, comparing equally successful patients with matched weight loss after LAGB and gastric bypass, are still needed to study the total and active ghrelin levels with an appropriate sampling technique, precise measures of the level of energy restriction or weight stability, and an assessment of vagal innervation. These studies should lead to mechanistic studies addressing the role of the vagus nerve in ghrelin changes after bariatric surgery.

Does ghrelin really matter for the outcome? If the increase of ghrelin levels after diet-induced weight loss is part of the endocrine changes in post-obese or weight-reduced obese individuals explaining weight regain, clearly the model of LAGB demonstrates that the role of ghrelin is not essential. Patients after LAGB, who do experience an increase in ghrelin levels in proportion to their weight loss, are able to maintain their weight loss, providing their band is adjusted, suggesting that other factors are involved in the postoperative control of appetite. The question of LRYGB remains unresolved as to the ghrelin levels after surgery. Whether acute changes in various gut hormones, including ghrelin, are predictors of the long-term success of the surgery, remains to be studied. Correlation studies have not yet suggested a clear role for ghrelin.

Should we still pay attention to ghrelin in the context of bariatric surgery? Since the discovery of ghrelin, numerous publications have converged to suggest that ghrelin is an important determinant of energy homeostasis, a peripherally secreted orexigenic hormone acting in key central pathways, with measurable levels demonstrating meal-to-meal variation. Surely, however, its effect after bariatric surgery will need to be assessed in parallel with other key hormones affecting gastric emptying, satiety, and meal termination, such as glucagon-like peptide 1, gastric inhibitory peptide, PYY, cholecystokinin, insulin, and leptin, among others, together with the newly discovered obestatin. Identifying additional anatomic and neurophysiologic mechanisms that modify ghrelin or other gut hormone levels after bariatric surgery and identifying the possible role of these changes in

the success of surgical weight loss procedures may prove extremely worthwhile for the understanding of human energy homeostasis and may help to develop more successful and less-invasive bariatric procedures in the future, as well as contribute to nonoperative therapeutic advances in treating obesity.

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