

## Mechanisms Responsible for Excess Weight Loss after Bariatric Surgery

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### Abstract

Obesity has increased alarmingly in the United States and is increasing in many countries of the world. Because obesity is an important risk factor for type 2 diabetes and other chronic diseases, it is important to develop approaches to counter the rapid increase in adiposity. One approach is bariatric surgery, the most successful clinical intervention known for treating obesity. Surgery can result in impressive weight loss and improvement of obesity-related comorbidities. Yet the mechanisms responsible for this remarkable effect of surgery remain controversial. It is now clear that caloric restriction, *per se*, does not explain all the reduction in stored fat mass after surgery. A number of gastrointestinal hormones, including glucagon-like peptide (GLP)-1, peptide YY, oxyntomodulin, GLP-2, glucose-dependent insulinotropic polypeptide, ghrelin, and others, can play roles in energy homeostasis and could be involved in bariatric-surgery-related weight loss and weight loss maintenance. Vagal innervation may play a role. In addition, there may be other yet-uncharacterized factors that could participate. This review discusses the possible roles of these hormonal mechanisms in various types of bariatric surgery to help elucidate some of the potential mechanisms at play in short-term and long-term post-bariatric surgery weight loss. Understanding such mechanisms could lead to new and efficacious means to control or even reduce the epidemic of obesity.

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### Introduction

Obesity is a worldwide epidemic that results in increased risk for type 2 diabetes, cardiovascular disease, cancer, osteoarthritis, nonalcoholic fatty liver disease, polycystic ovary syndrome, sleep apnea, depression, and reduced life expectancy.<sup>1</sup> Sixty-six percent of Americans are overweight or obese, and it is estimated that, if current trends continued, by 2048, all Americans would be

overweight or obese.<sup>2</sup> Moreover, the prevalence of child obesity has increased to alarming levels, with 17% of children and adolescents ages 2–19 years in the United States being obese.<sup>3</sup> The problem of obesity is not limited to the United States; according to the International Association for the Study of Obesity, there are 525 million obese adults worldwide and almost twice that number

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**Abbreviations:** (AGB) adjustable gastric banding, (AUC) area under the curve, (BMI) body mass index, (BPD) biliopancreatic diversion, (CCK) cholecystokinin, (DPP) dipeptidyl peptidase, (EWL) excess weight loss, (GB) gastric bypass, (GIP) glucose-dependent insulinotropic polypeptide, (GLP) glucagon-like peptide, (JIB) jejunum ileal bypass, (LAGB) laparoscopic adjustable gastric banding, (OGTT) oral glucose tolerance test, (PYY) peptide YY, (RYGB) Roux-en-Y gastric bypass, (SG) sleeve gastrectomy, (VBG) vertical banded gastroplasty, (VIP) vasoactive intestinal peptide

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overweight, which means that around 1.5 billion adults are overweight or obese and at risk for chronic diseases.<sup>4</sup>

Adiposity is controlled by a complex physiological system involving multiple feedback signals. Therefore, despite decades of sustained research, therapeutic options for obesity treatment are relatively limited. They include lifestyle interventions (such as diet, exercise, and behavioral changes), pharmacotherapy (orlistat for long-term treatment and phentermine and other sympathomimetics for short term) and surgical approaches (bariatric surgery). Both lifestyle interventions and drug therapy usually result in modest weight loss of 5–10%: meta-analyses show a decrease of approximately 2.5 kg at 24 months for diet, exercise, and lifestyle<sup>5</sup> and additional 2.8 kg compared with placebo for orlistat.<sup>6,7</sup> A great challenge to obesity management is maintaining the weight loss. Over the long term, one-third to two-thirds of dieters subsequently regain more weight than they lost on their diets.<sup>8</sup> While drug-treated patients are more likely to maintain weight losses, weight regain often occurs when medication is stopped.<sup>9</sup>

In contrast to these latter disappointing outcomes, bariatric surgery can be a very effective approach to weight loss. It is to date the most successful intervention for obesity. The weight loss range is 12% to 39% of presurgical body weight or 40–71% excess weight loss (EWL).<sup>10–12</sup> Moreover, bariatric surgery results in long-term maintenance of weight loss, as well as improvement in all obesity-related comorbidities.<sup>13</sup> In addition, bariatric surgery is the only approach to reversing type 2 diabetes mellitus, normalizing blood glucose even without significant weight loss.<sup>14</sup>

Because of efficacy, the number of bariatric surgery procedures is growing exponentially. It seems obvious that restriction of movement of food through the gastrointestinal tract might limit food intake and reduce fat storage, at least in the short term. However, the reduction in adiposity often exceeds that expected by the reduction in food intake *per se*. Mechanisms that result in impressive loss of stored fat due to surgery are far from totally understood. Therefore we have chosen to bring together much of the evidence related to bariatric surgery and loss of adiposity. We have limited this review to weight loss; there are excellent reviews related to bariatric surgery and normalization of glycemia.<sup>14,15</sup> There is little question that it is of great importance to understand the mechanisms associated with weight loss and bariatric surgery, in the hope that, eventually, therapeutic approaches that are less invasive than surgery itself can be developed.

## Bariatric Surgical Procedures

Based on the nature of intervention, bariatric surgery procedures can be divided in two main groups: purely gastric restrictive versus gastric bypass (GB) with intestinal transposition (Table 1; Figure 1).

### *Gastric Restrictive (Laparoscopic Adjustable Gastric Banding, Vertical Banded Gastroplasty, Sleeve Gastrectomy)*

Laparoscopic adjustable gastric banding (LAGB) is the most commonly performed bariatric surgery procedure performed worldwide. Together with the second most common, laparoscopic Roux-en-Y gastric bypass (RYGB), they accounted for 82% of the bariatric surgeries performed worldwide in 2008 (Table 2). It is estimated that 112,200 adjustable gastric banding (AGB) surgeries were performed in 2008 in the United States and 168,597 worldwide.<sup>16</sup> In LAGB, an adjustable silicone band is placed around the stomach just below the gastroesophageal junction, physically reducing gastric size and resulting in a pouch with an initial volume of about 15 ml. The lumen of the band is connected via tubing to a subcutaneous port, and injection of saline allows the band to be adjusted<sup>17</sup> (Figure 1D). Average weight loss post-LAGB, according to a meta-analysis, is 42.6% EWL at 1 year, 50.3% at 2 years, and 55.2% at >3 years postsurgery.<sup>12</sup> Another report indicates 59% EWL at 8 years post-LAGB.<sup>18</sup>

**Table 1.**  
Types of Bariatric Surgery Procedures

Procedure	Description
Purely gastric restrictive	
AGB/LAGB <sup>a</sup>	Adjustable silicone band is placed around stomach to create a 15 ml pouch
VBG	Rows of staples to create a stomach pouch and a band to allow food passage
SG	Resection of great curvature to create a tubular stomach
GB with intestinal transposition	
GB/RYGB <sup>a</sup>	15–30 ml gastric pouch + rerouting of nutrient flow through gastrojejunal anastomosis
BPD/BPD with duodenal switch <sup>a</sup>	Distal gastrectomy with the stomach anastomosed to distal ileum; proximal ileum is anastomosed to terminal ileum
JIB	Proximal jejunum is anastomosed to the terminal ileum

<sup>a</sup> A version of the main procedure.

Vertical banded gastroplasty (VBG) reduces stomach size by using both staples and a band to create a small gastric pouch. The pouch has a small opening through which food can enter the rest of the stomach. Vertical banded gastroplasty was introduced in 1980 and, in

its original form, had a relatively higher complication rate and lower success rates in weight loss than other procedures. MacLean's modification of the standard open Mason procedure resulted in a decrease in complication rate and a good weight loss, but the procedure is

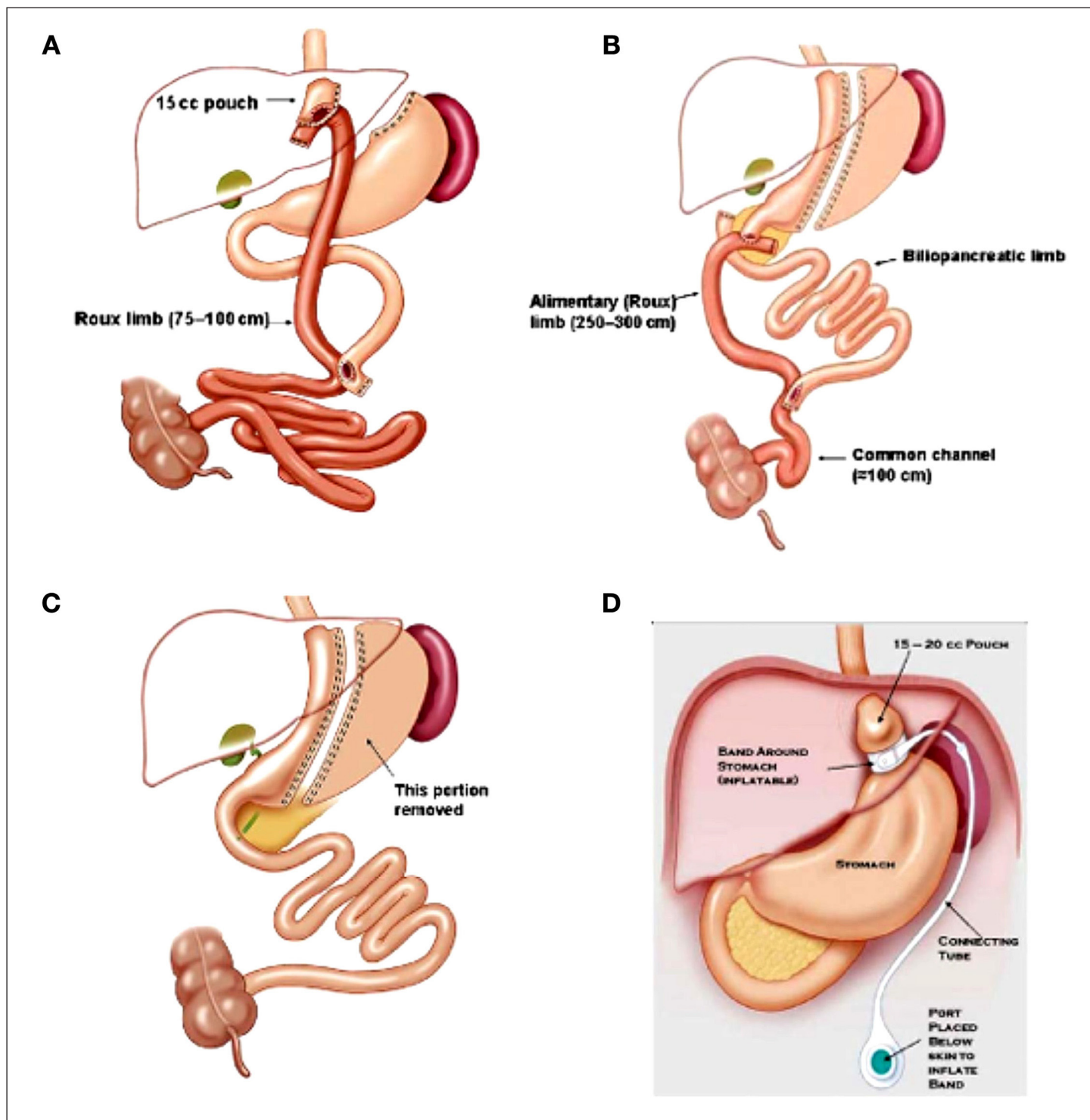


Figure 1. (A) RYGB, (B) biliopancreatic diversion with duodenal switch, (C) SG, and (D) LAGB. (Reproduced with permission from Annual Review of Medicine.<sup>23</sup>)

**Table 2.**  
Percentage Distribution of the Top Five Most Performed Bariatric Surgery Procedures Worldwide in 2008<sup>a</sup>

Procedure	Ranking	Percentage
LAGB	1	42.3
Laparoscopic standard RYGB	2	39.7
Open standard RYGB	3	5.7
Laparoscopic SG	4	5.1
Laparoscopic long-limb and very-long-limb GB	5	3.1
All others (<1% per type of surgery)	—	4.1

<sup>a</sup> Adapted from Pories and colleagues.<sup>14</sup>

infrequently used.<sup>19,20</sup> In 2008, VBG accounted for 1.1% of total bariatric surgeries performed worldwide.<sup>16</sup>

Sleeve gastrectomy (SG) was initially introduced as the first step of the duodenal switch procedure but is now used as a standalone procedure, frequently in the laparoscopic approach. The greater curvature of the stomach is resected, producing a tubular stomach that resembles the size and shape of a banana<sup>21</sup> (**Figure 1C**). The resection of the stomach fundus and antrum produce major endocrine changes. Thus SG shares several elements with GB and intestinal transposition procedures (discussed later), including postprandial increases in intestinal hormones such as glucagon-like peptide (GLP)-1 and peptide YY (PYY), as well as changes in ghrelin. As a result of technical efficiency and good EWL (approximately 66% at 3 years), the number of SGs performed has an upward trend: the percentage of SG performed worldwide has increased from none in 2003 to 5.4% in 2008.<sup>16</sup>

### ***Gastric Bypass and Intestinal Transposition (Roux-En-Y-Gastric Bypass, Biliopancreatic Diversion, Jejunum Ileal Bypass)***

In this group of procedures, stomach restriction is combined with rearrangement of various portions of the gastrointestinal tract such that nutrients are diverted toward the lower intestine while the upper intestine is bypassed.

Gastric bypass was first introduced in the 1960s.<sup>22</sup> Since then, there have been numerous advances in the technique, access, surgical equipment, and short-term and long-term outcomes. The most common version, laparoscopic RYGB, is the second most frequently performed bariatric surgery procedure, accounting for 39.7% of the 344,221 bariatric surgeries performed worldwide in 2008.<sup>16</sup>

In RYGB, the gastric volume is restricted by creating a 15–30 ml gastric pouch, while nutrient flow is rerouted from the stomach directly into the proximal jejunum through a gastrojejunal anastomosis, resulting in three limbs: a biliopancreatic limb (from ligament of Treitz to jejuno-jejunostomy, transmits bile and pancreatic juices to the jejuno-jejunostomy), an alimentary limb (jejunal Roux-en-Y limb anastomosed to the stomach), and a common channel (from enteroenterostomy to ileocecal valve,<sup>23,24</sup> **Figure 1A**). In a meta-analysis of weight loss post-bariatric surgery, Buchwald and colleagues<sup>11</sup> showed that GB resulted in an average weight loss of 43.5 kg, or approximately 61.6% EWL. Assessment was made at the time of changes in comorbidities (e.g., diabetes, cardiovascular disease), usually less than 2 years. However, in most studies included in the meta-analysis, weight loss outcome was not statistically different between assessments made at 2 years or less or more than 2 years. Another meta-analysis by Garb and associates<sup>12</sup> shows an average of 62.6% EWL for laparoscopic GB.

Biliopancreatic diversion (BPD), devised by Scopinaro,<sup>25</sup> consists of a distal gastrectomy with a long Roux-en-Y reconstruction where the enteroenterostomy is placed at a distal ileal level. Thus the bypassed portion of the duodenum includes the point of entry for biliary and pancreatic secretions, leading to a delayed mixing of food with biliopancreatic secretions.

More frequently performed than the Scopinaro procedure is BPD with duodenal switch, a version in which the Roux limb is anastomosed not to the stomach but to the duodenum, thus preserving the pylorus<sup>23</sup> (**Figure 1B**). Biliopancreatic diversion results in impressive weight loss of ~70% EWL, maintained at long-term follow-ups. However, it is not often performed, representing only 2% of total bariatric surgery procedures.<sup>16,25</sup>

Jejunum ileal bypass (JIB), a procedure in which proximal jejunum is anastomosed to the terminal ileum, was the first surgical approach to obesity treatment.<sup>26</sup> Jejunum ileal bypass is not used anymore because of numerous and sometimes severe side effects, such as protein malnutrition, vitamin and mineral deficiencies, renal failure, liver disease, and even death.<sup>27</sup> However, information derived from the changes in gastrointestinal hormones after JIB can be applied to increase knowledge about how currently used bariatric surgery operations work.

Most of the weight loss post-bariatric surgery occurs in the first 2 years after surgery, but there is some information regarding long-term weight loss. In the



Dutch Bariatric Surgery Group study, maximum weight loss of 70% EWL was achieved on average by 17 months, but only 45% of EWL was maintained 8 years after GB.<sup>28</sup> After laparoscopic gastric banding, average EWL was reported to be 30% at 9 or more years<sup>29</sup> and 50% at 8 years.<sup>18</sup>

Clearly, bariatric surgery is a highly efficacious approach to causing weight loss. It is therefore of great interest to examine putative mechanisms that may synergize reduced flow of nutrients through the gastrointestinal tract to understand why surgery is so effective.

## Mechanisms of Weight Loss

### Malabsorption

It was initially thought that bariatric surgery results in weight loss only due to restriction of caloric intake and malabsorption produced by diversion of nutrients from the duodenum (in the bypass type). Indeed, as a result of decreased food intake, reduced absorptive area, and decreased gastrointestinal secretions, as well as side effects of surgery such as vomiting and food intolerance, malnutrition is present in 30–70% of bariatric surgery patients. Malnutrition includes protein–calorie deficiency, vitamins (especially fat soluble vitamins but also B12 and C), iron, calcium, and zinc.<sup>23</sup> However, Pilkington and coworkers<sup>30</sup> showed that, during weight loss, fecal energy content did not change in obese men and women after JIB, Condon and colleagues<sup>31</sup> reported that only 21–31% of weight loss could be attributed to fat malabsorption, and Bueter and associates<sup>32</sup> found no increase in fecal mass, fecal calorie content, or inflammation in a rat model of RYGB.

These latter studies argue that malabsorption and inflammation are not the primary mechanisms explaining weight loss after bariatric surgery.

### Caloric Restriction Per Se

Caloric restriction *per se* was another mechanism postulated for bariatric-surgery-induced weight loss (reduction in food intake due to stomach size reduction). Caloric intake is dramatically reduced after bariatric surgery (to 200–300 kcal/day), and it is likely that it is primarily responsible for the initial postsurgical weight loss. Obese subjects lost equivalent amounts of weight compared to surgery when placed on matched reduced caloric diets for 1 or 2 weeks.<sup>33,34</sup> However, the amount of long-term weight loss that results from caloric restriction is small compared with bariatric surgery, typically 5–10%, and it takes longer to achieve.<sup>35</sup> A 10% weight loss took 6 weeks for RYGB patients versus 30 weeks for patients

in a nonsurgical group (hypocaloric diet and lifestyle intervention).<sup>36</sup> Comparisons between weight loss via surgery versus weight loss via diet-exercise-behavioral intervention must be carefully interpreted given that surgery dramatically reduces caloric intake while other types of interventions are harder to enforce. However, there is evidence indicating that a negative energy balance via caloric restriction is not responsible for all the weight loss in bariatric surgery and for maintenance of that weight loss. Pair feeding of sham-operated diet-induced obese rats to a RYGB group resulted in less durable weight loss.<sup>37</sup> Bariatric surgery results not only in decreased food intake, but also in changes in frequency of food intake (fewer snacks, less food per meal) and in food preference. Post surgery, patients have reduced preference for sweet and fat taste and for high-calorie foods.<sup>38</sup> Behavioral and electrophysiological studies in rats showed that GB alters central taste processing for sweet taste.<sup>39</sup> These latter findings suggest that additional mechanisms come into play in bariatric-surgery-induced weight loss. Indeed in both restrictive and bypass procedures, but especially in bypass type, changes in gastrointestinal hormones and in enteral neural connections occur, and these changes may play important roles in weight loss achieved.

Changes in gastrointestinal hormones resulting from bariatric surgery may not totally explain the effects of bariatric surgery on weight loss. It does appear likely that they explain some of the remarkable effects of surgery on weight loss. Therefore we reviewed herein much of the evidence in this field in an attempt to assess the role of hormonal changes on bariatric-surgery-induced adiposity reduction, remembering that this is a fast-moving area of research and that we can only provide a “snapshot” of available findings.

## Gastrointestinal Hormone Changes after Bariatric Surgery

The gastrointestinal tract, the largest endocrine organ in the body, is a complex neuroendocrine system. More than 30 known peptide hormone genes are expressed in the digestive tract, with more than 100 different hormonally active peptides produced.<sup>40</sup> Because they may play important roles in weight loss following surgery, it is of interest to review changes in hormones that have been investigated in relation to bariatric surgery. For each signal, it is important to examine the effects of bariatric surgery on changes in hormone levels at basal and after meals and compare these changes with changes induced by food restriction weight loss to ferret

out the role of surgery. Additionally, it is important to show that either reversal of observed changes or simulation of such changes can reiterate the effects of surgery. It is extremely difficult to accomplish the latter goals because of the different types of surgery involved, the many possible candidates promoting weight loss, and the effects on food intake and energy utilization. A summary of what we know so far follows.

## Glucagon-Like Peptide-1

Glucagon-like peptide-1 is a 30 amino acid peptide released from L-cells in response to meal ingestion. L-cell stimulation increases not only GLP-1 but also GLP-1-related peptides, all derived from the same proglucagon molecule: glicentin, oxyntomodulin, intervening peptide-2, and GLP-2, as well as PYY and perhaps glucose-dependent insulinotropic polypeptide (GIP).<sup>41,42</sup> GLP-1-releasing cells are located throughout the intestine, with a greater concentration in distal ileum and colon. In the upper intestine, colocalization of GLP-1 with GIP has been found,<sup>43</sup> while, in the lower intestine, GLP-1 colocalizes with PYY.<sup>44</sup> Thus it is very possible that any intervention that stimulates GLP-1-producing cells (bariatric surgery or secretagogues) would increase levels of these other hormones as well.

After release, GLP-1 is rapidly degraded by the ubiquitous enzyme dipeptidyl peptidase (DPP) 4. Glucagon-like peptide-1 is involved in multiple ways in glucose homeostatic regulation, as well as in energy balance through effects on satiety and food intake. Together with GIP, GLP-1 is a major insulinotropic hormone responsible for the incretin effect, enhancement of insulin secretion by oral glucose versus an isoglycemic intravenous load. Over the long term, GLP-1 increases beta-cell mass by stimulating beta-cell growth and proliferation and by inhibiting apoptosis. Glucagon-like peptide-1 also improves plasma glucose by inhibiting glucagon secretion and by slowing of gastric emptying and intestinal motility. Via the latter two actions, GLP-1 has a major role in the "ileal break" (the phenomenon whereby the presence of nutrients in distal gut results in a decrease in gastrointestinal motility); this, in turn, contributes to a feeling of fullness and reduces hunger and food intake.<sup>45,46</sup> Glucagon-like peptide-1 appears to promote insulin-independent glucose disappearance, an effect that may be mediated via a portal vein GLP-1 sensor. The mechanism of this latter effect is not known, but it is possible that portal presence of GLP-1 activates portal vein receptors that, in turn, via neural connections, result in increased glucose uptake in target organs such as liver, muscle,

or adipose tissue.<sup>47,48</sup> By acting on the central nervous system, GLP-1 inhibits food and water intake and promotes satiety. In the brain, GLP-1 is synthesized by a population of neurons in the nucleus of the solitary tract; their fibers project to other areas of the brain, in particular, the paraventricular and arcuate nucleus of the hypothalamus.<sup>49</sup> It is possible that peripheral GLP-1 also acts in the central nervous system by binding to GLP-1 receptors that are abundant in the so-called "leaky" areas of the blood-brain barrier (subfornical organ, area postrema, median eminence, and pituitary) by crossing the blood-brain barrier or by activating peripheral sensors that, in turn, communicate with brain areas involved in satiety and food intake regulation.<sup>50</sup> Indeed, a meta-analysis of studies investigating the effect of pharmacological dose intravenous GLP-1 on food intake found that GLP-1 reduced *ad libitum* caloric intake by 12% in normal or obese humans,<sup>51</sup> subcutaneous administration of recombinant GLP-1 to obese humans reduced caloric intake by 15% and produced weight loss.<sup>52</sup> The GLP-1 agonist, exenatide, which has a longer disappearance half-time than the native compound, inhibits food intake and promotes weight loss in many patients.<sup>46</sup>

A majority of studies indicate that plasma levels of GLP-1 can increase after bariatric surgery, but the effect on fasting plasma GLP-1 varies by surgery: increases in fasting plasma GLP-1 after RYGB, JIB, or SG;<sup>53-55</sup> no change after LAGB;<sup>56,57</sup> or even a decrease after AGB or RYGB.<sup>58</sup>

Perhaps more important than the fasting plasma GLP-1 to glucose homeostasis and food intake are postprandial plasma levels. Postprandial plasma GLP-1 increments have been reported as early as 2 days after RYGB<sup>59</sup> and 1 week post-BPD;<sup>60</sup> plasma GLP-1 is elevated as late as 3 years after RYGB<sup>61</sup> or 20 years after JIB.<sup>54</sup> There may be a progressive postprandial plasma GLP-1 increase after bariatric surgery, at least up to 24 months. Le Roux and coworkers<sup>62</sup> showed significant increases in plasma GLP-1 area under the curve (AUC) at 3 months and then at 12 and 24 months post-RYGB.<sup>62</sup> In contrast, Korner and colleagues<sup>63</sup> found no difference in 30 min plasma GLP-1 levels between 26 and 52 weeks post-RYGB, a finding that was supported by long-term studies of Vidal and associates.<sup>64</sup>

Surgical procedures with intestinal rearrangement (RYGB, BPD, and JIB, compared with AGB and VBG) result in larger increases in plasma GLP-1. The GLP-1 postprandial plasma levels were higher in RYGB than in AGB 6-36 months after surgery, even though weight loss in the two groups was the same. Importantly, the

increase in the RYGB group was higher than the lean controls, suggesting a supraphysiological change in hormone secretion pattern post-bariatric surgery.<sup>65</sup> Similar results were reported in other studies,<sup>66,67</sup> suggesting that the satiety effect of GLP-1 might be involved in the higher weight loss observed with RYGB. Fasting and postprandial plasma levels of GLP-1 were more increased 6 months after BPD than after VBG.<sup>53</sup> Korner and colleagues<sup>63</sup> found that postprandial GLP-1 did not change at 26 or 52 weeks after LAGB. However, Carroll and coworkers<sup>68</sup> showed that, 6 months after AGB, postprandial GLP-1 increased to levels comparable to those of a lean control group. The GLP-1 levels increase after SG as well. Peterli and colleagues,<sup>55</sup> in a longitudinal study looking at GLP-1 increases after RYGB or SG, found that postprandial plasma GLP-1 was higher in the RYGB group than in the SG group at 1 week postsurgery. However, by 3 months, the groups had similar levels of GLP-1.

Why does GLP-1 increase after bariatric surgery? Isbell and associates<sup>33</sup> measured plasma GLP-1 in response to meal test before and 4 days after RYGB or after 4 days of a reduced-calorie diet to match surgery group in nonsurgical obese subjects. Both groups lost similar amounts of weight, but plasma GLP-1 response was increased only in the surgical group. A similar finding was reported by Laferrère and coworkers,<sup>69</sup> and Marfella and colleagues<sup>70</sup> found similar postprandial GLP-1 increases post-BPD or a 10 kg weight loss through diet, but the interprandial plasma GLP-1 levels were higher in the BPD group. Available evidence suggests that a greater exposure of distal gut to nutrients post-bariatric surgery could result in higher GLP-1 secretion from the L-cells. Indeed, in animal models, ileal transposition, a procedure in which a portion of the ileum is transposed to the jejunum, thus changing the normal distribution of the endocrine cells, results in higher plasma levels of GLP-1 and PYY as well as weight loss.<sup>71</sup> Findings also support the hypothesis that direct delivery of nutrients to the lower intestine might play a role. McLaughlin and associates<sup>72</sup> report a case of a patient with hyperinsulinemic hypoglycemia and increased plasma GLP-1 levels after RYGB. Insertion of a gastrotomy tube in the remnant stomach and thus a change in nutrient delivery from the distal gut to the more physiological proximal gut resulted in reversal of abnormal GLP-1 and insulin secretion.

It seems clear that GLP-1 plasma levels are higher after surgery than after equivalent diet-induced weight loss. DPP-4 inhibition could also play a role in the increased GLP-1 levels seen after bariatric surgery. DPP-4 activity

was significantly decreased (and GLP-1 increased) after GB but not after caloric restriction.<sup>73</sup> But Lugari and coworkers<sup>74</sup> reported increased plasma DPP 4 activity post-BPD. Dipeptidyl peptidase 4 activity is different in diabetic patients versus non-diabetic patients, and this could explain why patients with and without diabetes post-RYGB have the same amount of weight loss but different GLP-1 profiles.<sup>75,76</sup> It does not appear that reduction in DPP 4 activity explains the postsurgery increase in GLP-1.

It is not sufficient to demonstrate increase in GLP-1 after surgery; it is not clear what role the hormone plays in bariatric-surgery-induced weight loss. Procedures with greater increases in plasma GLP-1 (RYGB, BPD) also have greater weight loss.<sup>63</sup> However, when patients post-BPD and post-VBG were compared at 6 months, despite significantly increased plasma levels of GLP-1 (19 times), the weight loss in the two groups was the same,<sup>53</sup> suggesting that GLP-1 plays only a modest role in the weight loss. Morínigo and colleagues<sup>75</sup> compared plasma GLP-1 levels and weight loss 6 weeks after RYGB and found that patients with or without diabetes had similar weight loss despite the fact that GLP-1 was increased in patients without diabetes and not increased in patients with diabetes. In contrast, de Carvalho and associates,<sup>77</sup> in a study investigating oral glucose tolerance test (OGTT) plasma GLP-1 levels 9 months after RYGB found that patients with abnormal glucose metabolism had higher levels of GLP-1 than normal glucose tolerance patients. These data do not make it possible to determine whether GLP-1 determines the weight loss process or is a result of it, and if the presence or absence of diabetes before bariatric surgery influences the relationship between GLP-1 and weight loss.

In attempts to clarify the role of GLP-1 in bariatric-surgery-induced weight loss, a number of researchers looked at changes in GLP-1 in relation to food intake, hunger, and satiety. Borg and coworkers<sup>78</sup> found increases in postprandial plasma GLP-1 at 1, 3, and 6 months after RYGB as well as reduction of hunger and increases in satiety but no changes in nausea or aversion to food. Morínigo and colleagues<sup>79</sup> found three-fold increases in plasma GLP-1 levels 6 weeks after RYGB but no correlation between GLP-1 changes and eating behavior. On the other hand, different findings were reported by Le Roux and associates<sup>59</sup> in a prospective study looking at postmeal levels of several gut hormones, including GLP-1, at 2, 4, 7, and 42 days after RYGB. The authors also measured hunger and satiety in “responders” (patients with significant weight loss postsurgery) and



“nonresponders” (patients with poor weight loss or weight regain). In all subjects, plasma GLP-1 increased immediately after surgery, and GLP-1 increases were significantly correlated with decreases in hunger score and increases in fullness score. Suboptimal responses to GLP-1 were associated with patients who had poor weight loss. Blockade of gut hormone release with somatostatin during a meal increased food intake in a GB group but not in a weight-loss-matched gastric banding group, suggesting that the GLP-1 response contributes to changes in food intake in the GB group but not in the banding group. It is important to mention, however, that somatostatin suppresses other gut hormones, such as PYY, GLP-2, and oxyntomodulin, and that any of these other hormones could contribute to the observed effects during the blockade. Interestingly, in a subsequent longitudinal study, the same group found increased satiety at 18 and 24 months post-RYGB without significant increases in plasma GLP-1.<sup>80</sup>

While GLP-1 increases after surgery, it remains to be proven that this increase plays an important role in the extra effects of bariatric surgery on weight loss, beyond reduction in food intake. Glucagon-like peptide-1 remains an excellent candidate via effects on satiety and food intake; increased peripheral GLP-1 as a result of nutrient rerouting to the lower intestine could be activating vagal afferents from the hepatoportal area and other parts of the gastrointestinal system or could activate brain neurons involved in satiety and food intake regulation via “leaky” areas of the blood–brain barrier. More research is necessary, with direct blockade of GLP-1 increase or signaling during bariatric surgery, in order to demonstrate a causal relationship between increases in GLP-1 and bariatric surgery weight loss. Nevertheless, as of this date, increased GLP-1 has not been firmly implicated in the beneficial effects of bariatric surgery *per se*.

## Peptide YY or Peptide Tyrosine Tyrosine

Peptide YY is a 36 amino acid member of the polypeptide family that also includes neuropeptide Y (found in the brain) and pancreatic polypeptide. Though part of a different peptide family, PYY has many similarities with GLP-1. Like GLP-1, it is released by the L-cells of the gastrointestinal tract, mainly in the ileum and colon, as well as by the brain. Peptide YY is cosecreted from L-cells with GLP-1 in response to meal stimulation (probably by both direct contact with luminal nutrients and via neural and endocrine mechanisms) and also degraded by DPP 4. Peptide YY inhibits gastric emptying

and intestinal motility, being part of the “ileal brake” together with GLP-1. Its active form PYY 3-36 inhibits food intake by binding to Y-2 neuronal receptors and inhibiting the release of neuropeptide Y.<sup>81–83</sup>

Most studies show that both fasting and postprandial plasma levels of PYY increase after bypass-type operations (RYGB and BPD)<sup>84</sup> but not after some of the restrictive type (LGB, VBG),<sup>85–87</sup> though one study found increased postprandial PYY levels at 6 and 12 months post-VBG compared with baseline.<sup>88</sup>

A few studies compared PYY changes after the same amount of weight was lost through various types of bariatric surgery or via lifestyle intervention and drug therapy. Valderas and colleagues<sup>89</sup> reported plasma PYY AUC increasing after both RYGB and SG (though more in the RYGB group) and decreasing in a nonoperated group. Hunger decreased and satiety increased significantly in the RYGB group, and satiety changes were correlated with plasma PYY changes. Other studies found that RYGB and SG result in similar weight loss and comparable increases in postmeal PYY in plasma.<sup>55,90</sup>

Similar to GLP-1, plasma PYY has been reported to be increased as early as 2 days after surgery for RYGB<sup>59</sup> and as early as 1 week after SG.<sup>55</sup> Plasma PYY levels continue to rise progressively for at least 6 months after surgery.<sup>78</sup> Twenty years after JIB, postprandial plasma PYY levels were still elevated in surgical patients compared with weight-matched nonsurgical obese.<sup>54</sup>

Several studies investigated the relationship between changes in PYY and eating behavior. Morínigo and associates<sup>75</sup> found significantly increased postprandial plasma PYY 6 weeks after RYGB compared with both baseline and weight-matched obese subjects. Surprisingly, the change in PYY (or GLP-1) did not correlate with changes in eating behavior parameters.<sup>75</sup> However, in a follow-up study looking at hormone levels 1 year after surgery, the authors found that a large plasma PYY response to a meal predicted a better weight loss outcome<sup>91</sup>. In a cross-sectional study comparing no-diabetic lean, post-RYGB, post-gastric banding, and obese weight-matched subjects, Korner and coworkers<sup>92</sup> reported postprandial increases in plasma total PYY and PYY 3-36 that were 2-4 times higher in RYGB than in all other groups. The RYGB group also reported greater satiety. Their data are consistent with the concept that the PYY rise promotes increased satiety and earlier meal termination and results in weight loss and maintenance of weight loss. Subsequently, in a prospective study, the Korner group<sup>63</sup>



showed that, at 1 year, there was greater weight loss in RYGB compared with gastric banding (30% versus 15%) and that the plasma PYY AUC was greater in the GB than in the banding group. Weight loss percentage was not correlated with the PYY AUC, but this could be explained by other hormones such as GLP-1 or ghrelin also contributing to weight loss.<sup>63</sup>

Little is known about the mechanism of PYY increase after bariatric surgery and the consequences on the weight loss process. Peptide YY increases after bariatric surgery but not after no-surgical weight loss, indicating that increases in PYY are related to the surgical procedure and not to weight loss *per se*. Moreover, since PYY plasma levels increase in GB (RYGB and BPD) but not in restrictive operations (AGB and VBG), it has been hypothesized that, in bypass-type operations, rapid delivery of nutrients to the distal gut could stimulate the L-cells with the resulting increases in GLP-1, PYY, oxyntomodulin, GLP-2, and other hormones.<sup>93</sup> Indeed, studies in rodents showed that RYGB results in increases in plasma GLP-2 and in proliferation of intestinal crypts; in humans, RYGB increases plasma GLP-2, a possible explanation for the absence of significant malabsorption but the continuation of weight loss.<sup>62</sup> Why then does PYY increase in a “restrictive” surgery like SG? The answer might be in transit time. While AG and VBG slow the passage of nutrients, it appears that SG increases gastric emptying, resulting in increased nutrient delivery and stimulation of distal intestinal cells.<sup>94</sup> Another hypothesis is that SG is associated with incomplete digestion due to decreased gastric acid secretion and that delivery to the duodenum of higher pH undigested chyme could result in increased PYY.<sup>90</sup>

Does increased PYY play a role in post-bariatric surgery weight loss? Obese subjects have lower fasting and meal-stimulated PYY levels than normal subjects,<sup>65</sup> and infusion of PYY 3-36 in humans has been shown to decrease hunger score and food intake,<sup>81</sup> so it is plausible that increased PYY levels contribute to weight loss.

Surgeries that result in higher plasma PYY levels, such as RYGB and BPD, are associated with greater weight loss.<sup>11</sup> Association does not prove causality, but several lines of evidence indicate that PYY may play a significant role: Morínigo and coworkers<sup>91</sup> showed that a large PYY response to a meal predicted a better weight loss outcome. Similarly, Le Roux and colleagues<sup>59</sup> showed that suboptimal PYY responses were associated with patients who had poor weight loss or weight regain at 25 months after RYGB. Infusion of blocking agent

somatostatin reduced hormonal response in post-RYGB patients and resulted in a doubling of the food intake the day of infusion. Interestingly, the same effect was not observed in gastric banding patients, suggesting that gut hormones do not play a role in weight loss after these types of operations. An animal study may shed some light into this issue: when GB surgery was performed in diet-induced obesity wild-type and PYYKO mice, there was no difference in weight loss between surgery and sham-operated mice in the PYYKO mice, though the wild-type lost weight with bariatric surgery.<sup>95</sup>

There is thus convincing evidence that PYY is one of the major hormonal contributors to post-bariatric surgery weight loss. Increased PYY resulting from bariatric surgery (via increased direct delivery of nutrients to the L-cells, decreased transit time, or high pH of undigested chyme) results in satiety, decreased food intake, and possibly changes in energy expenditure, leading to weight loss both in the early phase and over long term.

## Oxyntomodulin

Oxyntomodulin is co-secreted with GLP-1 and PYY from the intestinal L-cells in response to food ingestion. Cut from the larger proglucagon molecule, oxyntomodulin contains the entire glucagon sequence and a C-terminal extension. Like GLP-1 and PYY, it is an anorectic hormone; it also inhibits gastric acid secretion and motility.<sup>96</sup> Oxyntomodulin administration reduces food intake in both lean and obese individuals and reduces body weight.<sup>97,98</sup> Oxyntomodulin plasma levels in response to OGTT increased two-fold 1 month after GBP but not after an equivalent amount of weight was lost via diet.<sup>99</sup> The changes in oxyntomodulin correlated with changes in GLP-1 and PYY, so it is difficult to distinguish its effect from the effects of these other two hormones. Based on preliminary data coming from studies looking at changes in all products of the L-cells after bariatric surgery, it appears that oxyntomodulin would synergize with PY/GLP-1 to constitute a powerful hormonal triumvirate that contributes to postsurgical weight loss. At present, the possible involvement of this “L-cell triumvirate” is the most compelling hypothesis explaining the effects of bariatric surgery on weight reduction.

## Glucagon-Like Peptide 2

Glucagon-like peptide-2 is a 33 amino acid hormone secreted by L-cells in response to food intake, as well as neural and endocrine factors. Like GLP-1, it is cut from the larger proglucagon molecule. Glucagon-like peptide-2

does not directly affect food intake and satiety. However, GLP-2 has an important enterotrophic role by increasing crypt cell proliferation and increasing mucosal cell mass via inhibition of apoptosis and plays a critical role in response to enteral stress or injury.<sup>100</sup> Le Roux and associates<sup>62</sup> showed that postprandial GLP-2 plasma levels were increased in obese humans 1 month after RYGB surgery and peaked at 6 months. In a rodent study that complemented the human study, the authors showed that increased plasma GLP-2 levels were associated with crypt proliferation and increased intestinal mass.

The possibility that GLP-2 might contribute to long-term maintenance of weight loss via increasing the number of cells producing GLP-1 and PYY, and via gut proliferation that avoids malabsorption, offers an exciting area of investigation into the mechanisms of bariatric surgery-induced weight loss.

## Glucose-Dependent Insulinotropic Polypeptide

GIP is a 4- amino acid peptide secreted from the intestinal K-cells (located mainly in the duodenum and proximal jejunum) and released in response to nutrients, especially lipids. Shortly after release, the active peptide is inactivated by DPPV4. GIP has a strong insulinotropic action and, together with GLP-1, accounts for the incretin effect.<sup>101</sup>

GIP is much more involved than GLP-1 in lipid metabolism. A growing amount of data indicates that GIP is involved in lipid assimilation and storage, and thus can be directly linked to obesity. GIP knockout mice are resistant to development of obesity.<sup>102</sup> In animal models, antagonism of GIP receptor was able to prevent or reverse obesity and reduce hepatic and muscle lipid stores.<sup>103</sup> In humans, acute infusion of GIP increased abdominal subcutaneous adipose tissue blood flow, free fatty acid re-esterification, and triacylglyceron.<sup>104</sup>

There is more information after RYGB than after any other type of surgery with respect to GIP changes. Plasma GIP appears to decrease after RYGB; however, the results of different studies are not always in concordance. Laferrère and coworkers<sup>105</sup> found increased plasma GIP in response to an oral glucose load 1 month after RYGB in patients with diabetes. In contrast, Whitson and colleagues<sup>76</sup> measured no change in fasting plasma GIP 6 months after RYGB in obese individuals with and without diabetes, while Rubino and associates<sup>57</sup> found decreased fasting plasma GIP at 3 weeks in patients with diabetes

but no decrease in patients without diabetes. Contrary to these reports, Bose and coworkers<sup>87</sup> measured increased plasma GIP during an OGTT at 1, 6, and 12 months after RYGB in patients with diabetes.<sup>87</sup> However, in a cross-sectional study, Korner and colleagues<sup>67</sup> found that postprandial levels of GIP were reduced in RYGB compared with AGB or overweight controls, suggesting that a comparatively lower GIP could account for greater weight loss with RYGB (all subjects without diabetes).

More consistent is the GIP change after BPD. Salinari and associates<sup>106</sup> showed that, 1 month after BPD, plasma GIP AUC during an OGTT was decreased four times and was not significantly different from that of a lean control group.<sup>106</sup> Similar findings were reported by other groups.<sup>60,107,108</sup> Surprisingly, Näslund and coworkers<sup>52</sup> found increased plasma GIP levels 20 years after JIB compared with 9 months after surgery or compared with obese nonsurgical or lean subjects, but this finding was not replicated in other studies. With JIB, Lauritsen and colleagues<sup>109</sup> and Sarson and associates<sup>108</sup> found that GIP plasma levels were significantly reduced postsurgery.

There seems to be no decrease in GIP post-AGB or post-VBG. Shak and coworkers<sup>56</sup> showed no change in fasting plasma GIP at 6 or 12 months after AGB surgery, while Guldstrand and colleagues<sup>110</sup> found that, 1 year after surgery, plasma GIP AUC post-oral glucose challenge increased in VBG compared with JIB. No data regarding SG effects on GIP in humans are available at the time of this review.

From the current literature, an intriguing picture emerges of GIP having a potentially important role in maintaining weight loss after GB bariatric surgery. In the bypass-type of bariatric surgery, exclusion of the upper portion of the intestine, where the GIP-producing K-cells are located, would result in decreased exposure to nutrients of the K-cells, resulting in decreased levels of GIP. Lower GIP could contribute to less fat accumulation and result in weight loss or long-term weight loss maintenance.

## Ghrelin

A 28 amino acid peptide secreted by X/A-like cells in the stomach fundus and duodenum and, in smaller amounts, in the jejunum and ileum, ghrelin is an orexigenic hormone involved in short-term (meal-to-meal) and long-term regulation of food intake.<sup>111</sup> Plasma ghrelin increases preprandially and decreases after food intake.<sup>112</sup> Ghrelin secretion is stimulated by fasting and by hormones such

as cholecystokinin (CCK) and gastrin and inhibited by food intake, somatostatin, and growth hormone.<sup>111</sup> The mechanism of appetite stimulation by ghrelin involves actions in the neuropeptide Y/Agouti-related peptide neurons in the arcuate nucleus of hypothalamus.<sup>113</sup> Ghrelin is also involved in long-term regulation of energy homeostasis. Obese people are reported to have 27% lower fasting ghrelin than lean,<sup>114</sup> and in obese, ghrelin levels are less suppressed postprandially.<sup>115</sup> Chronic administration of ghrelin in rodents resulted in adiposity: peripherally administered ghrelin reduced fat utilization while intracerebroventricular administration reduced food intake.<sup>116</sup>

The role of ghrelin in weight loss post-bariatric surgery is difficult to assess. Studies employed different designs (cross sectional or prospective), different surgeries (LAGB, RYGB, BPD, or VGB), fasting or postprandial plasma levels, different intervals postsurgery, various levels of weight loss, as well as various assays to quantify ghrelin measuring either total or active ghrelin. There are currently over 100 original articles that look at ghrelin changes with bariatric surgery in humans, as summarized in several excellent systematic reviews.<sup>83,117–119</sup> Only a few studies are presented here, though all of them bring important contributions to understanding the complex changes in gastrointestinal hormones produced by bariatric surgery.

The first report of ghrelin changes after bariatric surgery is that of Cummings and colleagues.<sup>120</sup> They measured 24 h plasma profile of ghrelin 9–31 months post-RYGB and compared them with body mass index (BMI)-matched obese subjects who lost weight via dieting and with lean volunteers. After surgery, fasting, postprandial, and interprandial plasma ghrelin was lower compared with the obese or lean subjects: 77% lower than in normal weight controls and 72% lower than in obese weight-matched controls. There were no meal-related fluctuations and no diurnal fluctuations. These results were replicated in other cross-sectional studies.<sup>121–123</sup> In longitudinal studies, ghrelin has been shown to be changed as early as 1 day after surgery. However, different types of surgery appear to have opposite effects on fasting and postprandial ghrelin: GB operations tend to reduce ghrelin, while restrictive ones increase or do not change ghrelin (with the exception of SG). Ghrelin plasma levels were already reduced 1 day after RYGB<sup>124</sup> or SG but not after LAGB.<sup>125</sup>

Decreased fasting plasma ghrelin levels were found at 1 week, 3 months, and 6 months after RYGB and maintained to 2 years after surgery.<sup>55,126–128</sup> It appears

that RYGB results in permanent suppression of plasma ghrelin—most of the studies indicate that ghrelin levels are not changed in response to a meal<sup>90,129</sup> or that the postsurgery plasma ghrelin AUC is reduced.<sup>55</sup> Though, in many studies, plasma levels of ghrelin are reduced after RYGB, some longitudinal studies have found no change in fasting and postprandial plasma levels immediately after surgery (2–42 days)<sup>59</sup> or in 1, 3, and 6 months<sup>78</sup> or even in 24 h profile.<sup>130</sup> Others have found increases at 6, 7, and 12 months<sup>84,131,132</sup> or in consecutive measurements up to 1 year.<sup>133</sup> Dadan and associates<sup>134</sup> found that fasting plasma ghrelin decreased 1 day after RYGB, increased by day 7 though still lower than baseline, and were not different from baseline at 1 and 3 months.

It is possible that diabetes status affects ghrelin changes. Whitson and coworkers<sup>76</sup> found that postprandial plasma ghrelin increased post-RYGB in patients without diabetes but not in diabetes patients.

Twenty-four-hour ghrelin plasma concentrations were increased after BPD, and they lacked normal pulsatility.<sup>135</sup> However, BPD with duodenal switch, in which the gastric fundus is resected, resulted in a decrease in plasma ghrelin.<sup>136</sup> Other investigators also found reductions in ghrelin after BPD.<sup>12</sup>

In contrast to RYGB, gastric banding does not appear to reduce plasma ghrelin levels, which are not changed<sup>56,85</sup> or are increased.<sup>68,137</sup> In a prospective study that followed bariatric surgery patients for 52 weeks, fasting ghrelin plasma levels were increased at 26 and 52 weeks after LAGB,<sup>63</sup> while, in another prospective study, fasting plasma ghrelin was decreased one day after LAGB, was back to baseline at 7 days and 1 month, and increased from baseline at 3 months.<sup>134</sup>

Similarly, fasting ghrelin plasma levels are increased after VBG.<sup>128,136,138</sup> Foschi and coworkers<sup>129</sup> showed that VBG restores the mechanism of ghrelin regulation by nutrients since, after VBG, ghrelin was suppressed by a liquid test meal.

A special case of restrictive surgery with respect to ghrelin is represented by SG. Levels of ghrelin are reduced 1 day after SG and maintained low at 6 months.<sup>125</sup> Karamanakos and colleagues<sup>90</sup> showed that fasting ghrelin plasma levels were reduced at 1, 3, 6, and 12 months after SG and that, in addition, postprandial suppression of ghrelin was increased after surgery. Similar findings were reported by Peterli and associates.<sup>55</sup> In a prospective study, Bohdjalian and coworkers<sup>139</sup> showed that fasting



ghrelin plasma levels are decreased at 6 months and stay decreased 5 years after SG.

The mechanism of plasma ghrelin changes after bariatric surgery is not completely understood. Based on the location of ghrelin-producing cells, the restrictive component of bariatric surgery procedures, by reducing access of nutrients to ghrelin-producing cells, should decrease ghrelin levels and presumably result in satiety. On the other hand, it has been shown that weight loss by caloric restriction paradoxically results in increasing plasma levels of ghrelin, both in the fasting and in the postprandial state.<sup>120</sup> Frühbeck and colleagues<sup>140,141</sup> have conducted a series of studies in which changes in ghrelin were investigated when the same amount of weight was lost via RYGB, AGB, BPD, or diet. They found that surgeries that conserve the contact of nutrients with the stomach fundus (AGB, BPD) or weight loss via diet do not result in fasting plasma ghrelin decreases, while those that do not conserve the fundus (RYGB, gastrectomy) lead to a decrease in fasting plasma ghrelin. To test the hypothesis that nutrient contact with stomach fundus affects plasma ghrelin levels and the outcome of bariatric surgery, Pérez-Romero and associates<sup>142</sup> performed a prospective longitudinal 2-year study comparing patients who underwent either of two surgical procedures: RYGB that preserves food contact with stomach fundus (ringed RYGB) and one that does not (modified RYGB). There was no significant difference between groups, indicating that ghrelin increase does not depend exclusively on the contact with gastric fundus.

It has been suggested that the effect of bariatric surgery on the integrity of vagal fibers involved in ghrelin secretion might explain the interstudy differences. Sundbom and coworkers<sup>132</sup> measured fasting plasma ghrelin post-RYGB and plasma levels of pancreatic polypeptide, an indicator of vagal functionality. They found a remarkable correlation between variations in the two peptides, suggesting that certain surgical procedures that compromise vagus integrity might have an effect on ghrelin levels. However, Perathoner and colleagues<sup>143</sup> showed that, when patients with RYGB either did or did not have the anterior vagal trunk transected during surgery, there was no difference in postoperative weight loss, parameters of satiety assessment or plasma ghrelin between the two groups, discounting vagal involvement.

What is the evidence that plasma ghrelin changes are involved in bariatric-surgery-induced weight loss? Roux-en-Y gastric bypass and SG, procedures that result in ghrelin decrease, lead to better weight loss than LAGB,

in which ghrelin increases. However, despite significantly different ghrelin, weight loss with different surgeries can be identical.<sup>141</sup> Couce and associates<sup>144</sup> compared fasting plasma ghrelin and weight loss in patients after laparoscopic RYGB or after other laparoscopic gastrointestinal surgery. Plasma ghrelin fell in both groups 2 h after surgery and continued to be lower 10 days after surgery in the RYGB group but not in the control. However, by 6 months, plasma ghrelin levels were no longer low in RYGB or in the control group despite significant weight loss (body weight increased in the control). Busetto and coworkers<sup>145</sup> investigated whether fasting plasma ghrelin before LAGB was a predictor of weight loss 2 years after surgery. Patients were divided into two groups; one group that had higher ghrelin levels than expected based on BMI and the other group had normal ghrelin levels. Both groups had similar EWL percentages after surgery without any significant differences in band management. Uzzan and colleagues<sup>146</sup> showed that, 1 year after LAGB, serum ghrelin levels as well as ghrelin expression in cells of gastric fundus are increased despite significant weight loss. Other investigators have looked at the correlation between changes in ghrelin and how they correlate with changes in eating behavior. Dixon and associates<sup>137</sup> performed an experiment in which plasma ghrelin and satiety visual analog scales were compared in AGB patients who attended blind crossover breakfast tests, one with optimal band restriction and one with reduced restriction. Patients with optimal restriction experienced greater satiety, but there was no difference in ghrelin levels between the two groups. In RYGB patients, Christou and coworkers<sup>121</sup> looked at fasting plasma ghrelin in those who achieved successful weight loss (EWL 72%) and less than ideal weight loss (EWL 27%) 3 years after surgery. There was no difference between fasting or postprandial levels in the two groups and no correlation between ghrelin levels and their visual analog scale score.

From data presented here, it remains unclear whether ghrelin is involved in bariatric surgery weight loss. The type of surgery, time point after surgery, and integrity of vagal nerve might all play a part in determining the levels of ghrelin after surgical intervention. If ghrelin levels are decreased postintervention, it is possible that this has a contribution to weight loss, but low ghrelin levels is not a consistent outcome in bariatric surgery. It is possible that the change in ghrelin with bariatric surgery is an epiphenomenon and that other factors are involved in both the changes in hormone and in weight loss. Despite early excitement regarding the role of ghrelin, it seems that ghrelin is unlikely to be a major

player in bariatric-surgery-induced weight loss, though further research is needed to determine the precise effect of this hormone on energy homeostasis changes after bariatric surgery.

## Other Hormones

### *Obestatin: The Anti Ghrelin?*

Obestatin, a 23 amino acid peptide, is derived from the preproghrelin precursor. Obestatin is present in many tissues, including the gastrointestinal tract (gastric mucosa, duodenum, jejunum, colon, pancreas). Initially identified as a product of the ghrelin gene with opposite effects to those of ghrelin, obestatin is now believed to have many more actions, some of them similar to those of ghrelin. Fasting significantly reduces obestatin levels, and postprandial concentrations are inversely correlated with BMI.<sup>126,147</sup> The actions of obestatin in humans, as well as its role in regulation of food intake and energy homeostasis, are still controversial. Obestatin was reported to decrease food and water intake and body weight and to decrease intestinal motility in rodents,<sup>147</sup> however, later studies could not replicate these effects.<sup>148</sup> Little is known about obestatin's involvement in post-bariatric surgery weight loss. Haider and colleagues<sup>149</sup> showed that obestatin is lower in obese patients compared with lean controls and is increased 6 months after AGB. In contrast, Roth and associates<sup>126</sup> found that obestatin levels did not change 2 years after RYGB in spite of the massive weight loss of 62.5% EWL.

### *Cholecystokinin*

Cholecystokinin (pancreozymin) is produced in I-cells of the small intestine, mainly in the duodenum and in smaller amounts in the rest of the small intestine. Cholecystokinin stimulates pancreatic exocrine secretion and gall bladder contraction and inhibits gastric emptying and food intake.<sup>150,151</sup> No changes in fasting or postprandial CCK were seen after RYGB, VBG, or JIB.<sup>52,152,153</sup> One study found that, 120 days after VBG, the plasma CCK response to an acidified meal was faster and with a higher peak than before surgery, though the total AUC was not different.<sup>154</sup> Ockander and coworkers<sup>155</sup> found an increased density of CCK cells in the duodenal mucosa of patients post-JIB, but the significance of this finding is not clear.

### *Apolipoprotein A4 and Enterostatin*

Apolipoprotein A4 and enterostatin are two peptides secreted from the intestine during digestion and absorption of lipids and act as signals to reduce food intake.<sup>151-157</sup>

Fasting plasma concentration of apolipoprotein A4 was found to be increased after GB.<sup>158</sup>

### *Neurotensin and Motilin*

Neurotensin, is a neuropeptide secreted by N-cells of ileum in response to fat and a stimulator of pancreatic and intestinal secretion and inhibitor of motility. Motilin functionally counteracts neurotensin and is secreted by M-cells. The levels of both peptides are altered in obesity, and it has been shown that gastric banding normalizes their plasma concentration. However, it is not known whether they play a role in bariatric-surgery-induced weight loss.<sup>159</sup>

### *Vasoactive Intestinal Peptide*

Vasoactive intestinal peptide (VIP) is present in mesenteric ganglia and submucous and myenteric plexus of the intestinal wall, with the highest concentration in colon and ileum. VIP can affect gastrointestinal motility and intestinal secretions and thus influence nutrient absorption.<sup>160</sup> No changes in plasma VIP have been found after either RYGB or VBG.<sup>153</sup>

## Vagus Nerve

The vagus nerve and the neural connections between the intestine and the brain might play a significant role in bariatric surgery weight loss. Many gastrointestinal hormones are released in response to neural as well as nutrient or peptide signals, and hormonal effects could be mediated via a neural pathway. The vagus nerve innervates most of the gastrointestinal tract, so afferent sensory fibers are in close proximity to ghrelin-producing cells, L-cells of the intestine and other endocrine cells.<sup>161</sup> Cholecystokinin acts through vagal receptors,<sup>150</sup> and GLP-1 receptors have been found on the nodose ganglia.<sup>162,163</sup> In addition, GLP-1 might act via vagal fibers to inhibit stomach motility<sup>164</sup> and to reduce spontaneous meal size.<sup>165</sup>

During bariatric surgery, different surgical techniques impact vagal innervation in various ways. Vagotomy has been shown to block ghrelin's effects on food intake,<sup>166</sup> so it is possible that sectioning the branch of vagus nerve that innervates stomach fundus during bariatric procedures results in weight loss via a lack of ghrelin action. To test the hypothesis that vagal denervation might result in additional weight loss, Angrisani and colleagues<sup>167</sup> performed LAGS with and without truncal vagotomy. At 12 or 18 months postsurgery, there was no difference in BMI and EWL between the two groups.

Similar results were reported by Martin and Earle<sup>168</sup> for LAGB and by Perathoner and associates<sup>143</sup> for RYGB. In contrast, Kral and coworkers<sup>169</sup> had found that adding truncal vagotomy to VBG improved weight loss (51% versus 34% EWL). Moreover, in the study of Angrisani and colleagues,<sup>167</sup> even though there was no statistically significant weight difference between the two groups, patients with truncal vagotomy required less band adjustment and reported less hunger than the intact vagus group. In a rodent study, Bueter and associates<sup>170</sup> showed that preservation of the paraesophageal bundle of the vagus nerve during GB resulted in lower body weight and reduced food intake. Glucagon-like peptide 1 and PYY levels were increased after surgery, though they were not different with or without vagal preservation, suggesting that perhaps the hormones' action via the vagal pathway might mediate the weight loss.

## Bariatric Surgery and Gut Microflora

Evidence suggests that intestinal microbiota may play an important role in obesity and that bariatric surgery results in important changes in gut microbial community. The Firmicutes and Bacteroidetes are dominant, but their proportions are different in obese versus lean: there is a 50% reduction in Bacteroidetes on obesity and a proportional increase in Firmicutes.<sup>171</sup> Firmicutes and lactic acid bacteria are decreased post GB, while *Bacteroides/Prevotella* and *E. coli* are increased, an indicator of adaptation to starvation-like conditions. Another bacteria, *Faecalibacterium prausnitzii*, which is negatively correlated with inflammatory markers, has been reported to be changed after GB.<sup>172,173</sup>

## Bariatric Surgery and Type 2 Diabetes Remission

Although not the focus of this article, the impressive effect of bariatric surgery on type 2 diabetes remission deserves special mention. Pories and coworkers<sup>14</sup> were among the first to draw attention to the astonishingly beneficial effect of bariatric surgery on glucose homeostasis and to the almost "magical" diabetes remission. Almost all (82.9%) of type 2 diabetes patients with adequate follow up after RYGB maintained normal levels of plasma glucose at an average 7.6 years postsurgery. Numerous subsequent studies have confirmed their findings.

It was initially thought that the improved glucose homeostasis after surgery is the obvious result of weight loss, as significant weight loss improves insulin resistance and contributes to diabetes management. Subsequent studies

have shown that the improvement in glucose homeostasis after bariatric surgery often occurs before significant weight loss. In addition, the positive effect of surgery on glucose tolerance exceeds that after an equivalent amount lost via diet and exercise.<sup>15</sup> Interestingly, a limited number of pilot studies have examined the effects of bariatric surgery in nonobese patients. Geloneze and colleagues<sup>174</sup> showed that, 6 months after duodenojejunal exclusion, nonobese patients with diabetes did not have any significant change in body weight, yet they had significant reductions in fasting glycemia and hemoglobin A1c. Similar results were reported 12 months after laparoscopic SG with duodenojejunal bypass in nonobese patients with diabetes with little weight loss.<sup>175</sup> It is likely that, in nonobese individuals, energy homeostasis is less impaired than in obese individuals; therefore bariatric surgery will not result in significant weight loss. Despite similar weight, glucose homeostasis is markedly improved by bariatric surgery, suggesting an additional mechanism for glycemia improvement versus weight reduction *per se*. There appears to be a distinct pattern in type 2 diabetes resolution after various types of surgeries: AGB seems to have less of an effect than the diversion types (RYGB and BPD) in which the nutrient flow is rerouted, intestinal continuity is disrupted, and the neuroendocrine connections of the gut with other organs are modified.<sup>152</sup> In these two latter types in particular, it has been postulated that an increase in nutrient delivery to distal gut results in an increase in hormones levels such as GLP-1 that positively impacts glucose homeostasis.<sup>93,176</sup> This hypothesis, termed the "hindgut" theory contrasts with the "foregut" theory, in which bypassing of the duodenum results in the exclusion from nutrient contact and subsequent release of a putative diabetogenic hormone. This, in turn, would result in lower levels and/or action of this factor, leading to improvements in glucose homeostasis. Whether this factor is an "antiincretin,"<sup>151</sup> gut glucagon,<sup>177</sup> or a yet undiscovered duodenal factor remains to be determined. It is possible that a factor impairing glucose utilization evolved over time as protection against postprandial hypoglycemia.

## Concluding Remarks

So how does bariatric surgery result in weight loss? Although caloric restriction seems to be the dominant mechanism in the early period, over the long term, reduction in body weight and maintenance of weight loss appear to be due to both a primary caloric restriction and to the rearrangement of hormonal and neural elements of gastrointestinal tract, resulting in secondary changes



in food intake (increased satiety, increased satiation, appetite suppression, aversive conditioning due to negative side effects).

Both exclusion of proximal intestine and increased nutrient delivery to the lower gut are probable mechanisms for inducing the hormonal changes associated with bariatric surgery. Stimulation of L-cells results in increases in PYY, GLP-1, and oxyntomodulin and results in decreased food intake. Exclusion of proximal gut leads to decreased levels of GIP (with favorable effects on fat deposition), lower ghrelin (less appetite), possibly lower gut glucagon, and a decrease in a yet undiscovered gut "x factor" that is obesogenic and diabetogenic. It is likely that several mechanisms are responsible for the bariatric surgery changes, including the concerted action of all modified enteral endocrine signals. Synergistic action of increased PYY and GLP-1 and possible other L-cells products, combined with reductions in GIP and ghrelin, the trophic role of GLP-2, all may contribute to a negative energy balance and consequent weight loss. In addition, modified neural signaling from the enteric nervous system and to various organs and tissues can contribute to hormonal changes directly or via enhancing or inhibiting hormonal actions. Of course, if there is a yet-unidentified factor, the role of the now-known factors could be less than expected.

The search for the mechanisms underlying the astonishing effects of bariatric surgery recapitulates the history of endocrinology, wherein unexplained physiological mechanisms lead to identification of important hormones and neural mechanisms. Research into mechanism of action of bariatric surgery offers exciting new opportunities to define the role of well-known hormones, explore the effect of less characterized ones, and perhaps discover new molecules involved in body weight regulation that may be useful for the treatment of patients. It is important to recognize that this research is an ongoing process, and we are likely just beginning to understand much about the role of the gastrointestinal tract in body weight regulation. It appears likely that additional not-yet-identified signals will emerge, and those signals may be even more important in explaining the effects of bariatric surgery. One is reminded of the effects of pancreatectomy observed serendipitously by von Mering and Minkowsky, ultimately resulting in the discovery and isolation of insulin. The effect of bariatric surgery on body weight is a phenomenon as striking as pancreatectomy was on the blood sugar in dogs. Careful research and application of the scientific method, with well-defined animal models and human research, will ultimately

allow us to disentangle this puzzle and develop new and important therapies.

The so-called "obesity epidemic" requires that the scientific and clinical research communities understand and exploit the mechanisms of bariatric surgery in the hope that therapies can be developed wherein surgery becomes unnecessary.

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