Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy:
understanding weight loss and improvements in type 2 diabetes after
bariatric surgery

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Scott WR, Batterham RL. Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy: understanding weight loss and improvements in type 2 diabetes after bariatric surgery. Am J Physiol Regul Integr Comp Physiol 301: R15–R27, 2011. First published April 6, 2011; doi:10.1152/ajpregu.00038.2011.—Obesity increases the likelihood of diseases like type 2 diabetes (T2D), heart disease, and cancer, and is one of the most serious public health problems of this century. In contrast to ineffectual prevention strategies, lifestyle modifications, and pharmacological therapies, bariatric surgery is a very effective treatment for morbid obesity and also markedly improves associated comorbidities like T2D. However, weight loss and resolution of T2D after bariatric surgery is heterogeneous and specific to type of bariatric procedure performed. Conventional mechanisms like intestinal malabsorption and gastric restriction do not fully explain this, and potent changes in appetite and the enteroinsular axis, as a result of anatomical reorganization and altered hormonal, neuronal, and nutrient signaling, are the portended cause. Uniquely these signaling changes appear to override vigorous homeostatic defenses of stable body weight and compelling self-gratifying motivations to eat and to reverse defects in beta-cell function and insulin sensitivity. Here we review mechanisms of weight loss and T2D resolution after Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy bariatric surgery, two markedly different procedures with robust clinical outcomes.

obesity; mechanisms; ghrelin; PYY; GLP-1

Obesity is one of the most rapidly increasing worldwide health care challenges, confronting the medical and scientific community and governments. While the incidence and mortality rates for cancer and heart disease are stable or falling in the United Kingdom and United States (21a, 137a, 147, 176), the incidence of persons overweight [body mass index (BMI) >25 kg/m²] and obese (BMI >30 kg/m²) is increasing dramatically. Currently, 61% of the adult United Kingdom population are overweight or obese (80), with 24.5% being obese (80) despite a target of <10% set out by the United Kingdom House of Commons Select Committee in 1992 (76a). In the United States >30% of adults are obese (144). This figure is estimated to increase to 50% by 2030 in the United States (211), and the United Kingdom is predicted to follow suit. Globally it is estimated that there will be 1.12 billion obese adults by 2030 (87). The prevalence in the hazardous extremes of obesity [morbid obesity (BMI >40 kg/m²); super obesity (BMI >50 kg/m²)] is increasing even faster (188). This problem is not unique to adulthood; in the United States 17% of children are obese (144), a further 30% will be by 2030 (211), and 75% will become obese adults (182).

Obesity carries significant morbidity and mortality (14, 55, 83, 220). It is a major risk factor for type 2 diabetes (T2D), hypertension, dyslipidemia, atherosclerosis, heart failure, cancer, liver disease, obstructive sleep apnea, infertility, degenerative joint disease, depression, and dementia (21, 154, 214). Reduced life expectancy is directly proportional to BMI (53) and, shockingly, obesity may have contributed to a reduction in overall life expectancy in the United States (5).

Obesity arises when energy intake chronically outweighs energy expenditure (134). Adoption of a Western lifestyle largely explains the dramatic global rise in obesity, by promoting overconsumption of energy-dense food and physical inactivity. Nonetheless, obesity has a high heritability (142). Despite difficulty finding causative genes, those identified through rare monogenic obesity and genome-wide association studies implicate the brain (112, 209), indicating that obesity is primarily a neurobehavioral disorder rather than a disorder of adipose tissue. However, sick fat or adiposopathy, the accumulation of mitochondrial dysfunction, endoplasmic reticulum stress, and inflammation, is central to obesity-associated metabolic disease, leading to disturbed insulin and leptin signaling, with dysregulation of central appetite control (4, 47, 79, 142). Yet, apart from the rare Mendelian disorders like leptin deficiency, presently we have little explanation for why some people develop the hazardous extremes of obesity.
Here we review the mechanisms proposed to mediate the weight loss and improvement in T2D after bariatric surgery, specifically Roux-en-Y gastric bypass (RYGB), laparoscopic sleeve gastrectomy (LSG), and relevant animal models. The topic of bariatric surgery as a whole, the control of appetite and energy homeostasis, and gut hormones are not covered in detail as these are well-reviewed elsewhere (26, 52, 85, 134).

**Failure of Medical and Success of Surgical Weight Loss**

**Medical management.** Therapeutic lifestyle actions like dieting and exercise and weight loss drugs deliver modest long-term weight loss in obese individuals (221). For example, in the prospective Swedish Obese Subjects Study, diet and conventional medical treatment, without use of drugs, resulted in a 1.6% increase in weight over a 10-yr period (180). Highly intensive dieting and an exercise program are capable of yielding significant weight loss; however, this is almost ubiquitously transient (74, 200). Pharmacological options are currently very limited. Absorption inhibitors, like orlistat, typically only reduce weight by 3 kg (149), and side effects are common and unpleasant; appetite suppressants, like sibutramine and rimonabant reduce weight only by 4–5 kg (149), but neither are currently available in the United Kingdom or the United States, due to heterogeneous actions within the central nervous system and potentially harmful consequences. Drugs in development are some years away from implementation (149). Explanations for this failure include a robust homeostatic appetitive response to calorie deficit and compelling hedonistic and addictive drives to eat, which not only oppose weight loss but also promote weight regain after substantial weight loss (134, 184, 193).

**Surgical management.** In contrast, bariatric surgery is highly efficacious and durable in yielding weight loss. In a meta-analysis of 621 studies, encompassing 135,246 patients and four distinct procedures, mean total weight loss was 38.5 kg and mean %excess body weight loss (%EWL) was 55.9% (27). %EWL is calculated from the equation: (weight loss in kg/ excess weight in kg) × 100; where excess weight = total body weight – ideal body weight. Furthermore, complete resolution of T2D occurred in 78.1% of patients, verified by improved biochemical parameters (27). Likewise dyslipidemia improves in 70%, hypertension in 61.7%, and obstructive sleep apnea in 85.7% (26); cancer incidence is significantly reduced, attributable to risk reduction in women but not men (108); and psychosocial well-being is enhanced (44, 72, 197). Despite surgical risk, bariatric surgery for morbid obesity is robustly associated with decreased overall mortality (3, 181).

Surprisingly, weight loss and resolution of T2D is heterogeneous and specific to the type of surgical procedure (Table 1). Conventional mechanisms like intestinal malabsorption and gastric restriction do not fully explain differences in weight loss, and potent changes in appetite are the portended cause. Furthermore, improved glycemic control is, in part, independent of weight loss magnitude and caloric restriction. Thus energy and glucose homeostasis alter in an operation-specific fashion, which may be determined by intestinal factors.

### Table 1. Efficacy and mortality data* after Roux-en-Y gastric bypass, biliopancreatic diversion, and adjustable gastric banding

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Roux-en-Y Gastric Bypass</th>
<th>Biliopancreatic Diversion</th>
<th>Adjustable Gastric Banding</th>
</tr>
</thead>
<tbody>
<tr>
<td>%EWL</td>
<td>59.5%</td>
<td>63.6%</td>
<td>46.1%</td>
</tr>
<tr>
<td>T2D Resolution</td>
<td>80.3%</td>
<td>95.1%</td>
<td>56.7%</td>
</tr>
<tr>
<td>Operative mortality at 1 mo</td>
<td>0.5%</td>
<td>1.1%</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

*Outcome data from Buchwald (27), Table 8; mortality data from Buchwald (26), RESULTS. EWL, excess weight loss; T2D, type 2 diabetes mellitus.

**The Gut, Energy Homeostasis, and Obesity**

Energy homeostasis is a complex biological process by which food intake and fuel expenditure are constantly adjusted to preserve stable long-term balance (134). This involves central assimilation of short-term as well as long-term hormonal, neural, and nutrient signals concerning energy status, which emanate from the gastrointestinal tract, adipose tissue, and hepatic stores. The net result is a level of appetite or satiety and of energy expenditure, which is integrated with cognitive, visual, olfactory, and taste cues to provide volition for active food seeking and exertion.

Surgical reorganization of gut anatomy causes changes in nutrient partitioning and absorption, and hence local stimulation, with resultant adaptation of short-term and possibly long-term hormonal, neuronal, and nutrient signals. These signaling changes modify appetite, energy consumption, and gut motility, and uniquely they appear to override vigorous homeostatic defenses of stable body weight and compelling self-gratifying motivations to eat. Unexpectedly through surgical modulation of gut anatomy, the previously unsolvable obesity pandemic may be solvable, and the previously irreversible natural history of T2D may be reversible. This makes study of gut function the vanguard for understanding obesity and T2D pathology and design of obesity and T2D drugs.

**RYGB and LSG as models for understanding weight loss.** Weight loss surgery is classified as restrictive, malabsorptive, or hybrid, involving aspects of both. RYGB is a hybrid surgical procedure (Fig. 1) endorsed as having the best balance of efficacy and risk by the National Institutes of Health (27). Biliopancreatic diversion (BPD), another hybrid procedure, is modestly more efficacious but less safe, while adjustable gastric banding (AGB), a purely restrictive procedure, is less efficacious but safer (Table 1). Hence RYGB is the commonest bariatric procedure in the United States and Canada (28) and the fastest growing procedure in Europe (28). The frequency of use of RYGB and the magnitude of appetite and glucoregulatory benefits make it an excellent choice for mechanistic studies.

Laparoscopic sleeve gastrectomy (LSG) is a restrictive bariatric procedure, designed originally as a first stage procedure to reduce weight in the super obese (who have a high operative risk), which could be transformed into a hybrid procedure such as RYGB, following sufficient weight loss (Fig. 1). The medium-term efficacy of LSG is superior to laparoscopic AGB (LAGB) (1, 146, 168) and can rival RYGB, with EWL of 63–75% and T2D resolution of 82–84% documented (1, 82, 84, 105, 207). However, as with other restrictive procedures
est endocrine organ in the body (52, 129). Changes in gut homeostasis is extensively regulated by the intestine, the largest endocrine organ in the body.

Changes in energy deficit, meal and snack frequency reduces and predilection for sugary and fatty foods diminish (40, 69, 88). This is evidenced by inferior glycemia, and the food deprivation-induced elevation of plasma ghrelin (8, 23, 43, 109, 122, 217). Alternatively, acute caloric restriction has been proposed as contributory, as this modestly decreases serum ghrelin levels (41, 42, 111), but this mechanism is unlikely given the contrast between bariatric operations.

Mechanisms of Weight Loss After RYGB

RYGB combines gastric restriction and intestinal bypass (Fig. 1). It does not produce clinically significant malabsorption (121), but weight loss magnitude is equivalent to procedures that do (26), and superior to purely restrictive procedures (26). By comparison with purely restrictive procedures, RYGB can produce up to 50% greater EWL (143). Animal models of RYGB indicate that this additional weight loss is not due to subclinical intestinal malabsorption, which accounts for only 4%, but due to decreased food consumption (189). Postoperatively, subjects experience a potent reduction in appetite, extending beyond the early postprandial period (24) during which gastric mechanoreceptors exert satiating effects. Despite energy deficit, meal and snack frequency reduces and predilections for sugary and fatty foods diminish (40, 69, 88). This is accompanied by rapid amelioration of T2D independently from weight reduction (170, 216), as evidenced by inferior glucose-regulatory effects following comparable weight loss from dieting or restrictive surgery (103, 152).

It is increasingly clear that central energy and glucose homeostasis is extensively regulated by the intestine, the largest endocrine organ in the body (52, 129). Changes in gut hormones, like ghrelin, peptide YY (PYY), and glucagon-like peptide-1 (GLP-1), follow RYGB and generally support anorexia and euglycemia.

Ghrelin. Ghrelin, uniquely, is the only orexigenic gut hormone. However, the regulation and action of ghrelin, in relationship with other energy signals, is incompletely understood (Box 1). After dieting and restrictive bariatric procedures, fasting ghrelin levels increase in proportion to weight loss (42, 70, 95, 135, 141, 185). Therefore, a profound elevation in fasting ghrelin might be anticipated following RYGB, which produces proportionately more weight loss. On the contrary, fasting ghrelin levels change heterogeneously and may decrease, not change or increase (160). These heterogeneous changes in ghrelin following RYGB may be partially due to timing of ghrelin measurement after surgery and partially procedural.

There is mounting evidence for an immediate reduction in ghrelin following RYGB (20, 95, 131, 133, 191), and there is some indication that this change is intraoperative, most sizably at division of the stomach (117). An explanation for this is transient vagal inhibition during surgery (117, 191), with heterogeneity resulting from inconsistent vagal manipulation (114). The vagus nerve plays an important role in ghrelin physiology, with afferent vagal tone being implicated in ghrelin functionality, and efferent vagal tone in ghrelin release (pharmacological and surgical inhibition of vagal neurotransmission in humans and animals abolishes both the stimulatory effect of peripheral ghrelin administration on eating behavior, and the food deprivation-induced elevation of plasma ghrelin levels) (8, 23, 43, 109, 122, 217). Alternatively, acute caloric restriction has been proposed as contributory, as this modestly reduces serum ghrelin levels (41, 42, 111), but this mechanism is unlikely given the contrast between bariatric operations. Another explanation for a reduction in fasting ghrelin is divi-
sion of the stomach to create a gastric pouch, given the importance of functionality of the gastric fundus for ghrelin secretion (57, 58), with variability resulting from differences in pouch configuration (157).

In the months after RYGB, fasting ghrelin levels appear to increase relative to immediate postsurgical levels (191). Weight loss is an important determinant of this, and one study directly correlates increases in fasting ghrelin with reductions in BMI at 6 and 12 mo after RYGB but not earlier (222). Nonetheless even at equivalent levels of weight loss, fasting ghrelin levels are highly variable. Early studies of RYGB demonstrate this adroitly; some demonstrate an increase in fasting ghrelin levels compared with presurgical level in the context of significant weight loss (61, 76, 206); others show lower or unchanged fasting ghrelin levels in the context of similar weight loss (39, 51, 54, 57–59, 63, 84, 92, 95, 110, 114, 115, 117, 118, 131, 145, 164, 185, 198, 215), and therefore should be viewed as absolute or relative falls in ghrelin secretion, respectively (in general these studies commenced ghrelin measurements beyond 6 mo after surgery and thus fail to show an initial fall in fasting ghrelin). This heterogeneity could result from variations in compensatory ghrelin hypersecretion and magnitude of weight loss, in combination with the antagonistic effect of surgery. Heterogeneity could also be a consequence of intrinsic phenotypic differences like insulin resistance, which independently predicts fasting ghrelin level (124). Moreover, variations in methodology may be contributory: different ghrelin assays produce inconsistent results (161), sample collection and storage is not standardized between studies, and some studies measure acyl (active) ghrelin while others measure total (acyl and des-acyl) ghrelin. Importantly, in studies reporting increases in fasting ghrelin, weight loss is as less profound in those with higher fasting ghrelin levels (222).

These findings suggest that circulating ghrelin levels are determined by a composite of potentially opposing surgical and weight loss consequences, and also multiple acute effectors. Quantifying the effect of ghrelin or correlating changes in ghrelin with weight changes will therefore require systematic analyses and modeling in large robustly matched cohorts. This should be achievable given the volume of bariatric procedures performed. Obtaining tissue for gene expression and using knockout (KO) and knockin animal models will further quantify the specific role of ghrelin. An increase in fasting ghrelin level in the months after surgery suggests that other, possibly more important, signaling changes are likely.

PYY. PYY3-36 is a potent anorectic hormone (Box 1). Dysregulation of PYY is implicated in obesity (12), and PYY secretion in response to feeding may be blunted in obese individuals (12). This is not replicated in all studies (165, 205), perhaps because of phenotypic variation. However, in obese individuals, sensitivity to the anorectic effect of PYY3-36 is intact (52).

After RYGB meal-stimulated PYY increases significantly (92, 115, 130, 132), varying between 1.5- and 10-fold, depending on meal caloric content (19, 33, 95, 133, 164). This occurs as early as day 2 after RYGB, and before weight loss occurs (110), indicating this is a direct consequence of surgery, and equivalent weight loss from dieting (203) or LAGB (19) does not similarly alter PYY. The most likely cause for this difference is surgical rerouting of gut content.

One explanation is that after RYGB nutrients enter a limb of distal jejunum directly from a small stomach pouch (Fig. 1), expediting delivery of nutrient-rich chyme to L-cells in the distal gut, and stimulating greater PYY secretion. Similar rerouting bariatric procedures replicate this PYY finding (86). Ileal transposition (IT) in rodents provides mechanistic support (Fig. 1). By transferring a section of resected ileum into the proximal duodenum, early nutrient exposure achieves similar augmentation of PYY secretion and reduces food intake and weight (186, 187). Gastric restriction, malabsorption, and foregut exclusion do not occur at IT, indicating that the causal surgical maneuver here, and seemingly after RYGB, is connecting the distal gut to the stomach (36, 90, 91, 187).

Another explanation is gut adaptation with enteroendocrine cell hypertrophy or hyperplasia. In rodents, RYGB increases bowel width, villus height, crypt depth, and crypt proliferation, maximal in nutrient-stimulated regions (194), and BPD (18) and IT (186) behave similarly. In humans, jejunoileal bypass has been shown to result in enteroendocrine cell hyperplasia (25). Interestingly, some but not all studies show small time-dependent incremental increases in PYY level following RYGB, consistent with an adaptive response to prolonged stimulation (95). These gut adaptations may only sometimes manifest clinically, feasibly in good responders (133). Gut adaptation, however, is not rapid and does not explain the early dramatic RYGB effects.

After RYGB, visual analog scales (VAS) consistently demonstrate an increase in satiety and a decrease in hunger in association with levels of PYY known to modify appetite (115). VAS is a measurement instrument used to quantify a subjective measure, for example appetite, in an objective format by asking a respondent to specify their level of agreement with a statement by indicating a position along a continuous line between two endpoints (e.g., Q: How hungry do you feel? A: Not hungry at all. to A: As hungry as I have ever felt.). While this might imply causality, most studies do not correlate changes in PYY with VAS (92, 94, 130, 203). One explanation is inadequate statistical power, as VAS scores lack sensitivity (19). Alternatively PYY, in isolation, may not fully explain appetite changes after RYGB.

Support for the involvement of PYY in RYGB-mediated weight loss is provided by good and poor surgical responder studies. Inferior weight loss after RYGB is associated with significantly lower stimulated PYY as well as GLP-1 levels (110, 133). However, many studies do not directly correlate changes in PYY and weight loss (19), but suffer from methodological problems including small numbers, use of weight surrogates for adipose mass, and the capricious nature of isolated gut hormone measurements. A recent animal model of gastrointestinal bypass provides direct evidence that PYY plays a key mechanistic role in surgical weight loss. Weight loss in diet-induced obese mice is greater after bypass surgery than after sham surgery; however, in obese PYY KO mice, weight loss is equivalent after bypass surgery and sham surgery (where weight loss results from caloric restriction and surgical stress but not anatomical modulation) (34). Nonetheless, a comparison of RYGB and IT in rats showed greater reduction in food intake and weight following RYGB, despite similar PYY enhancement (35), suggesting other important contributory factors. Thus PYY may play a principal role in synergy with other gut hormones uniquely affected by RYGB, includ-
ing reciprocal changes in ghrelin. Measuring changes in hormone ratios instead of isolated gut hormone levels might establish correlation with weight outcomes.

**Incretins.** Incretins are hormones secreted from the gastrointestinal tract, with potent insulinotrophic activity, glucoregulatory and energy homeostasis controlling functions, and, additionally, they are the key mediators of the enteroinsular axis (Box 1). T2D is characterized by defective insulin secretion and sensitivity, but the incretin effect is also impaired, mainly as a result of blunted GLP-1 secretion and glucose-dependent insulinoergic peptide (GIP) resistance (10, 20, 99). The immediate weight loss-independent T2D resolution after RYGB suggests that surgery modifies the enteroinsular axis.

The changes in systemic GLP-1 levels after RYGB are well documented. Meal or glucose stimulated GLP-1 responses increase early (110), durably, and by five- to 10-fold in magnitude from presurgical levels in nondiabetics and diabetics alike (37, 93, 115, 130, 132, 136, 204). GLP-1 levels do not change similarly following weight loss by dieting (103) or LAGB (19, 93, 95, 164, 178). After RYGB, fasting levels of GLP-1 do not appreciably alter (19, 37, 95, 101, 103, 130, 166). Thus, as with PYY, the rapid delivery of nutrient-rich chyme to the hindgut is the proposed primary stimulus, and in support of this, GLP-1 secretion also increases after IT (186, 187).

In contrast with PYY, incremental increases in stimulated GLP-1 levels over time are not observed (95, 99, 110), suggesting that gut adaptation does not augment GLP-1 secretion. Nevertheless the rare late complication of RYGB, hyperinsulinemic hypoglycemia, could be a consequence of either enteroendocrine cell or islet cell hyperfunction, as nesidioblastosis (abnormal islet cell histology accompanying this hyperinsulinemia) is not a ubiquitous finding (195).

Altered gut motility is another possible mechanism. Accelerated gastric emptying and intestinal transit have been demonstrated following RYGB, with GLP-1 level magnitude correlating with gastric emptying time (130). Other studies report delayed gastric emptying to solids (77, 137) and faster emptying to liquids (77) following RYGB, but the interpretation of these findings is complicated because GLP-1 itself slows gut transit. Notably, however, changes in PYY level do not correlate with gastric emptying time (130), casting doubt on this mechanism.

After RYGB, there is an early weight-independent increase in glucose-stimulated oxyntomodulin level, another important incretin originating in L-cells (Box 1), which strongly correlates with GLP-1 and PYY, suggesting concordant L-cell secretion (102). To date there has been no assessment of whether this effect persists.

Meal-stimulated GIP levels may increase transiently after RYGB (101, 103), and then normalize or fall (37, 67, 93, 100), but results of studies of stimulated and fasting GIP levels are inconsistent. GIP is predominantly secreted in the bypassed duodenum (10), making a sizeable role in weight loss and diabetes resolution doubtful in theory. In practice, however, GIP levels do appear to paradoxically fluctuate after RYGB, necessitating further clarification.

In association with increases in incretin levels after RYGB, patients with T2D show improved control, with reduced glycemic excursion after oral glucose, and return of the incretin effect on insulin secretion and of the first-phase insulin response to the level of nondiabetic obese controls (100, 101). Weight loss does not cause these glucoregulatory changes following dieting or LAGB (20), and GLP-1 antagonist administration in rats following RYGB inhibits GLP-1 secretion and reverses improvements in glucose tolerance (89). Moreover, lower fasting glucose and insulin levels and increased insulin sensitivity also follow RYGB (132, 156, 158, 166, 170, 216), and notionally GLP-1 contributes to this through inhibition of gastric emptying, restoration of insulin sensitivity, and inhibition of glucagon secretion (10). The exact role of these other basic incretin functions will require more detailed study, as highlighted by reports of failure to suppress, or discordant increases in blood glucagon levels after RYGB, in the face of antagonistic increases in GLP-1 (65, 103). Nonetheless, dramatic weight loss is also a key determinant of fasting improvements (99), due to a reduction in adiposity, inflammation, glucotoxicity, lipotoxicity, and altered circulating adipokines and cytokines.

Postprandial GLP-1 responses following RYGB reach the supraphysiological levels required to reduce energy intake and weight in humans (10). Oxyntomodulin administration to animals and humans also causes weight loss by reducing food intake in combination with increasing energy expenditure (119, 218, 219), and early indicators suggest a rise in meal-stimulated oxyntomodulin after RYGB. However, long-acting therapeutic incretins (e.g., exenatide and liraglutide) for T2D produce only modest weight reduction (1.5–3 kg) (10), nothing like the magnitude of RYGB. While not directly comparable, it is likely that incretins play a supportive or synergistic but not dominant role in RYGB weight loss.

Of note, gut hormone receptors are widely conserved throughout the gut and ANS, and gut hormones may act locally near their site of release to produce some of their effects (Box 1). For this reason measuring systemic gut hormone levels may not accurately reflect the contribution of local gut hormone activity on appetite, weight loss, beta-cell function, and insulin sensitivity. Thus, measuring levels of gut hormones in the portal circulation would be of great interest, and might resolve some of the discrepancies between systemic gut hormone levels and outcome.

**Cholecystokinin, amylin, and others.** Other gastrointestinal hormones including cholecystokinin, amylin, and pancreatic polypeptide have no clearly defined role in weight loss and T2D resolution after RYGB to date (143, 159, 160).

**Leptin and insulin sensitivity.** The appetite changes and weight reduction after RYGB occur in the face of a dramatic antagonistic homeostatic response to negative energy balance. Leptin, the archetypical satiety factor, is a long-term energy signal secreted in proportion to adipose tissue mass (9). It controls feeding behavior, substrate partitioning, and substrate metabolism through negative feedback at central homeostatic centers (113). When body weight reduces, leptin levels fall, and central pathways increase hunger and food intake and decrease energy expenditure as a result. When lean individuals gain weight, the converse occurs. This mechanism fails in the obese due to central leptin resistance (196). Equivalent central insulin resistance similarly deregulates energy homeostasis, and in combination with peripheral insulin resistance deregulates glucose homeostasis (45, 169). Indeed insulin and leptin resistance share pathological mechanisms in the brain (174, 196, 223). Acute caloric intake is also a major determinant of...
leptin level, and fasting causes a larger reduction in leptin than would be predicted after a short-term loss of adipose tissue mass alone (64). Leptin is also produced in the stomach, and may act locally via leptin receptor activation on vagal afferents or through systemic release to mediate this effect (162).

After RYGB leptin levels fall (51, 63, 92), and in this context, a marked reduction in satiety and increase in caloric intake would be expected. Significantly, this homeostatic response does not manifest. Furthermore, in some studies, reductions in leptin level do not directly correlate with weight loss or fat mass loss, suggesting an independent cause (19, 94). Moreover, greater reductions in leptin level have been suggested after RYGB rather than after LAGB, despite equivalent weight loss (19), while in obese rats leptin levels fall as early as 1 wk after duodenal exclusion surgery, prior to significant weight changes (148). This may be because BMI is a deficient surrogate for adipose mass or because leptin levels also reflect energy usage regardless of adipose tissue mass (64). RYGB reduces weight more rapidly than LAGB, and, proportionately, negative energy balance is greater despite quantitatively similar weight loss. Also, early after surgery, subjects are in negative energy balance, potentially lowering leptin levels before weight loss. In support, weight-stable women adjusted for weight loss and total adipose mass have similar leptin levels after RYGB and LAGB (96). Alternatively, leptin sensitivity could improve after RYGB (19), thereby explaining the absence of appetitive behavioral and weight-conserving responses.

Weight loss independent reductions in fasting glucose, fasting insulin, and insulin resistance occur early after RYGB (123, 156, 216). Isolated foregut exclusion in bariatric models also improves glucose homeostasis (167), and intestinal gluconeogenesis is a recently proposed mechanism for this beneficial foregut effect. In murine models, intestinal gluconeogenesis increases glucose fluxes in the portal vein, which are signaled to the hypothalamus via neural circuits and result in decreased food consumption and improved insulin sensitivity (127, 128, 151, 210). In addition, RYGB in mouse models increases intestinal gluconeogenesis with associated beneficial effects on food intake and fasting glucose homeostasis, while gastric banding does not. These effects are abolished in glucose transporter-2 KO mice with portal vein denervation (199). It is not clear what happens to leptin sensitivity in these models.

Other signaling pathways. Parasympathetic nervous signals via vagal afferents provide discrete information regarding nutrients in the gut and portal circulation, and food storage in the liver and adipose tissue (113, 174). Vagal efferents control motility and nutrient partitioning in the intestine and nutrient utilization for energy or storage. Furthermore, the ANS may affect long-term energy homeostasis, through primitive memory mechanisms like synaptic plasticity (134). New approaches in animals are delineating a mechanistic role for the ANS in RYGB outcomes; variable vagus sparing during surgery decreases postoperative food intake independently from gut hormone changes (29).

Short-term nutrient fluctuations also affect nervous signaling (38, 134, 174), and anatomical modification after RYGB may alter nutrient absorption and intestinal nutrient metabolism. These nutrients act directly on hypothalamic neurons to affect feeding behavior (104). Furthermore, free-fatty acid metabolites like oleoyl ethanolamide and long-chain fatty acyl CoA, produced in the duodenum in response to lipid ingestion, signal through vagal neurocircuits, to control feeding behavior (173) and hepatic insulin sensitivity (210). If these regulatory mechanisms are stimulated by undiluted bile acids or nutrient reflux into the excluded duodenum or have downstream lipid sensors, then they could play an important role in RYGB efficacy (195).

After RYGB, patients report a profoundly reduced preference for sweet and fat tastes, unexplained by common taste effectors (193). Rodents following IT develop conditioned taste aversion (186) and following RYGB respond more positively to low-sucrose foods, with subsequent reduction in pursuit of calorie-rich foods. This implies that gustatory pathways change after RYGB, and also that this may alter food reward value (179).

Different gut microfloral phyla are associated with lean, obese, and postbariatric phenotypes (30, 116, 201). Although the cause of this is uncertain, obese gut-derived microflora can generate obesity in germ-free mice (202). Potential mechanisms include increased lipopolysaccharide production (177), altered energy harvesting (202), and hormonal modulation (32). Conversely, dietary composition can change gut microflora, and diet is significantly altered after surgery (208). It remains to be seen whether changes in microflora play a contributory role in either obesity pathogenesis or in weight loss after bariatric surgery, or whether changes in microflora result directly from differing dietary contents (or a combination of both).

Learning from RYGB failures. Despite excellent efficacy, failure rates after RYGB are significant; durable weight loss is not achieved in 20% (26, 120), T2D improves without resolving in 15% (26), and more recent studies highlight recurrence of T2D after postsurgical resolution (48). Ascertain how those putative signaling changes alter in RYGB failures could clarify which are the necessary effectors for weight loss and T2D resolution.

Retrospective epidemiological studies associate a number of presurgical phenotypes and postsurgical behavioral factors with poor outcomes for weight loss and T2D resolution. Preoperative associations for inferior weight loss include T2D and male gender; postoperative associations include poorer follow-up attendance, lower levels of physical activity, unmarried status, poor self-esteem and abnormal eating behavior (120, 126). Preoperative associations for lack of T2D resolution include higher BMI, longer T2D duration, more severe T2D, larger number of T2D medications, and insulin use; postoperative associations include weight loss failure and weight regain (48, 170, 171). Causation is not established, but a number of basic mechanistic inferences are possible: 1) RYGB outcomes are complex, and failure most likely results from overlapping but heterogeneous causes; 2) presurgical phenotypes influence outcome, implying a core biological underpinning to failure mechanisms; 3) postoperative behaviors influence outcome, so the potential exists for behavioral override of RYGB mechanisms; and 4) postsurgical weight loss outcomes and T2D resolution are intrinsically linked but not directly correlative, meaning either that causal mechanisms are shared or improvements in one drive improvements in the other (or both), but that nonshared pathways also exist.

In T2D resolution, presurgical phenotype is essential, and poor outcomes associate with features consistent with beta-cell malfunction (48, 170, 171). Thus signaling changes in isolation
Mechanistic Review of Gastric Bypass and Sleeve Gastrectomy

Mechanisms of Weight Loss After LSG

The importance of gut hormones in mediating weight loss and resolution of T2D after RYGB is clear. This suggests that other efficacious bariatric procedures may behave similarly, and after LSG, changes in gut hormones occur and favor anorexia and weight loss.

Ghrelin consistently decreases following LSG (46, 84, 98, 107, 153, 212), and in contrast does not change or increases after other restrictive procedures (49, 57, 59, 71, 117, 141, 172). A prospective comparison shows ghrelin reduction at 1 and 12 mo following LSG, but increased ghrelin proportionate to weight loss following LAGB (107). This fall is particularly significant because the superior weight loss following LSG compared with LAGB would be expected to promote increased ghrelin levels (107). A head-to-head comparison of LSG and RYGB shows a fall in fasting ghrelin level after LSG and an unchanged fasting ghrelin level after RYGB despite equivalent weight loss (84). Moreover, falls in ghrelin following LSG are durable to 5 yr after surgery (17). A single study in rats supports a reduction in ghrelin after sleeve gastrectomy and an increase in ghrelin after gastric banding (212). However, in this study hypothalamic growth hormone secretogogue receptor-1a protein levels increase after sleeve gastrectomy, but do not change after gastric banding, suggesting increased ghrelin sensitivity following LSG. This may explain the comparable weight changes in both the surgical groups, and could challenge the proposed role of ghrelin in LSG weight loss, if ghrelin sensitivity increases as ghrelin levels fall.

Removal of ghrelin secreting tissue is one proposed mechanism for reduction in ghrelin after LSG. Gastric resection and removal of ghrelin secreting tissue is the major difference between LSG and other restrictive procedures that do not lower ghrelin levels. In support, a comparable reduction in ghrelin is observed following total gastrectomy (6). The importance of complete fundus resection at LSG is highlighted in a single case of high postoperative ghrelin and complete weight regain, where at reoperation a remnant of herniated fundus was found (106). Furthermore, in studies combining complete gastric fundus removal at LSG with IT or BPD, a fall in ghrelin is demonstrable (46, 97, 98), and this fall does not occur after isolated IT and after BPD without complete fundus removal (2, 57, 62). Theoretically residual fundus tissue could adapt and hypersecrete ghrelin (106). An auxiliary role for vagal interruption in ghrelin downregulation is anatomically unlikely given the caudal pathway of both anterior or posterior vagal trunks and the vertical, not horizontal, stomach transection.

Unexpectedly, changes in anorectic distal intestinal hormones follow LSG, in the absence of intestinal manipulation. Increases in meal-stimulated PYY levels occur at 1 wk after LSG (153), are sustained at 12 mo (84, 203), and can be equivalent to those after RYGB (84, 153, 203). Corollary changes in meal-stimulated GLP-1 are observed, but are less marked than after RYGB (84, 153).

Hindgut exposure through faster gastric emptying, which expedites sequential nutrient delivery to the duodenum, jejunum, and ileum, does not provide a convincing mechanism for these PYY and GLP-1 changes. Studies examining gastric emptying after LSG are discordant, and LSG with antrum removal increases emptying to solids (125), while LSG with antrum preservation has no effect (13). Interestingly, gastric antrum preservation is one hypothesis for outcome variability following LSG (60). Alternatively, duodenal nutrient sensing is sufficient stimulus for PYY secretion (155), and less well-digested chyme delivering greater stimulus for PYY secretion is one possible cause.

A direct role for LSG in leptin regulation needs more investigation. One animal study shows significantly lower plasma leptin levels after sleeve gastrectomy compared with paired sham-operated rats (183). Corresponding changes in hypothalamic leptin and melanocortin-4 receptor expression are not sufficient to resolve T2D but residual beta-cell function appears necessary.

In humans, putative biological mechanisms for weight loss failure have been investigated in good and poor human responders, as discussed previously. Good responders to RYGB achieve significantly higher nutrient-stimulated PYY and GLP-1 levels than poor responders (110, 133), but a direct correlation between change in weight and change in PYY and GLP-1 is not seen. One explanation is deficient powering due to small numbers and inadequate phenotyping; poor responder groups combine inadequate weight loss and weight regain, with their potentially different root causes. However, BMI itself is also an important predictor of gut hormone levels, and poor PYY and GLP-1 response may purely reflect a higher current BMI. In this context, a causal role for gut hormones in RYGB failure remains unsubstantiated.

Studies in rodents endorse a biological basis. In a mechanistic study, diet-induced obese rats after RYGB, when compared with sham-operated ad libitum-fed rats and with sham-operated rats pairfed to match the RYGB arm, failed to achieve durable weight loss at a similar frequency and in a similar pattern to human equivalents (68). At reintroduction of a solid diet, caloric intake was greater in RYGB failures than in successes. Furthermore, weight loss in RYGB failures was inferior to successes, but equivalent to the pairfed cohort, and superior to the ad libitum group. Thus RYGB successes lost more weight than pairfed counterparts despite equivalent caloric intake, and RYGB failures lost comparable weight to pairfed counterparts despite greater caloric intake. Seemingly, in this model, RYGB successes and failures either expend more energy (are less able to conserve energy), or utilize less ingested calories than shams controls. Thus the fundamental difference between failure and success may be retaining (or regaining) the capacity to compensate caloric deficit and weight loss by overeating.

In the same study, plasma PYY and hypothalamic PYY expression levels in RYGB failures were significantly lower than in the successes (68), but as the rats were culled in the fed state but in a nonstandardized manner, the timing between last feed and PYY measurement is potentially highly variable between the two groups and causation is unreliable. Also energy expenditure was greater after RYGB (successes and failures) than sham-operated (pair- and nonpairfed), a finding replicated in separate studies and in other animal models (189).

The study of RYGB failure mechanisms may yet prove highly informative, but given the greater levels of complexity in humans, it may be prudent to investigate failures in rodent models first, then replicate findings in much larger, prospectively investigated human cohorts, employing subgroup analyses in extreme good and poor responders.

Review
and sensitivity to intraperitoneal leptin were not observed (183), suggesting no reduction in leptin resistance.

In obese patients with T2D, LSG causes early and significant improvements in glucose homeostasis, prior to weight loss (207). Acute caloric restriction causes some, but not a comparable improvement in obese controls with T2D undergoing laparoscopic cholecystectomy (163), and thus is not the primary mechanism. Furthermore, foregut exclusion plays no mechanistic role in LSG. Observed gut hormone changes after LSG support glycemic improvement, but whether these alone or in conjunction with acute caloric restriction are sufficient for early T2D resolution is unclear. Of these changes, augmented GLP-1 response is likely to have the most substantive insulinogenic and glucoregulatory effects, and increases in postprandial insulin secretion accompany LSG (153). Ghrelin also exerts several diabetogenic effects (22, 23, 190), so a reduction, coupled with an increase in PYY may improve glucose homeostasis (16). Unquestionably, the enormity of weight loss maintains and strengthens long-term T2D resolution.

Gastric restriction is a key additional weight loss mechanism after LSG. The importance of gastric restriction is highlighted by significant weight loss after other restrictive procedures like LAGB, which yield lesser gut hormone deviations (27). In head-to-head comparison, LSG produces ~10–15% greater EWL than LAGB (146, 212). LSG reduces gastric volume to 10% of its presurgical volume (150). This can be predicted to restrict food intake and activate stretch mechanoreceptors earlier, to terminate eating (satiation). In addition the potential of the removed gastric fundus to form a pseudo pouch and permit larger food volumes is lost. Currently there is no evidence that reducing bougie size, the major operative determinant of sleeve diameter, improves weight loss (56, 82). Nonetheless sleeve diameter also varies by proximity of staple line application and mechanical tissue stretch around the bougie (150), and late sleeve dilatation may be more common when larger bougie diameters are employed (213), one proposed mechanism for weight regain following LSG.

Perspectives and significance

Significance. RYGB and LSG robustly reduce weight and improve T2D, while anatomical modifications at RYGB and LSG alter gut hormones in a procedure-specific fashion. By implication, gut hormone changes are a fundamental difference between these and other less efficacious bariatric procedures. After RYGB, augmentations of meal-stimulated PYY and GLP-1 are robust, while a general reduction of fasting ghrelin (or failure in the setting of weight loss to maximally increase) is likely. After LSG, augmentations of meal-stimulated PYY and GLP-1 and reduction of fasting ghrelin level are apparent but will require further replication in larger cohorts. Whether gut hormone changes are sufficient in isolation to explain the dramatic clinical outcomes that accompany these procedures remains uncertain. The role of other signaling changes, including neuronal, nutrient, and microfloral modification, within this complex regulatory system should not be underestimated.

Perspectives. Many outstanding questions require further investigation. Perhaps the most important of these is how and where these signaling changes have their effect. Calorie restriction is a potent stimulus for increased appetite, and following most restrictive bariatric procedures subjects consume more frequent small volume energy-dense meals (24). After LSG and RYGB this adaptive response is not observed (193). The role of gut hormones and other signaling changes that accompany RYGB and LSG might be to negate homeostatic centers that increase meal frequency during caloric deficit and positively alter food reward centers, thus preventing obesogenic eating behaviors. Animal and human studies demonstrate this adroitly. In rats, combining chronic food restriction on top of LSG increases meal frequency (183). This implies that appetite and not physical restriction prevents adaptive increases in meal frequency and that the ability to overeat remains, but is reset to defend a lower energy threshold. In humans, following RYGB and LSG, brain regions relevant to eating behavior imaged by positron emission tomography CT show decreased dopamine (DA D2) receptor availability, reflecting an increase in dopamine levels (50). This links well-known gut hormone influences on dopaminergic neurotransmission to functional alterations in reward centers following bariatric surgery.

DISCLOSURES

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