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Abbreviations in this Article

BMI: body mass index
DS: pancreatico-biliary bypass with duodenal switch
GLP-1: glucagon-like peptide-1
LAGB: laparoscopic adjustable gastric band
NPY/AGRP: neuropeptide Y/agouti-related peptide
PYY: peptide tyrosine tyrosine (YY)
RYGB: Roux-en-Y gastric bypass

BARIATRIC SURGERY

How Gut Hormones Help Weight Loss after Bariatric Surgery

ABOUT TWO-THIRDS OF U.S. RESIDENTS ARE OVERWEIGHT, and of those, nearly half are obese.[1(CP ref.)] Alarmingly, subgroups growing the fastest include Americans with BMI ≥ 35 kg/m^2.[2 (CP ref.)] Recent studies have shown a positive association of BMI and relative risk of death, independent of other risk factors such as smoking and preexisting disease (in individuals 50–71 years of age).[3 (CP ref.)] Whereas behavioral and pharmacologic interventions designed to promote weight loss remain the mainstay of treatment, surgical interventions to reduce caloric intake have become an important therapeutic option, particularly in certain clinical settings. The basic and clinical science underpinnings of bariatric surgical procedures are the focus of this month's Tri-Point article.

Basic Researcher Perspective

➤ By Roy G. Smith, Ph.D.

Dr. Smith is professor and chair of the Department of Metabolism and Aging at The Scripps Research Institute, Jupiter, Fla.

Highlights

- Benefits of RYGB are mediated by increased secretion of gut peptides.
- RYGB exaggerates postprandial increases in GLP-1 and PYY_{3-36}.
- Gut peptides cholecystokinin and pancreatic polypeptide are not reproducibly increased after RYGB.
- Ghrelin secretion does not play a dominant role in explaining RYGB's benefits.
- RYGB benefits are consistent with higher secretion of GLP-1 and PYY_{3-36} from L cells.

The most commonly used bariatric surgery procedures are the Roux-en-Y gastric bypass (RYGB) and laparoscopic adjustable gastric band (LAGB). They were designed to reduce weight in severely obese subjects (defined by a BMI ≥ 40 kg/m^2) by restrictive and malabsorptive mechanisms. However, changes in malabsorption appear to be transient and precede the adaptation associated with an increase in peptide tyrosine tyrosine (PYY). RYGB has become the preferred procedure in the United States, with a success rate of about 80%. Intriguingly, even before significant weight loss, this procedure improves glucose tolerance and insulin sensitivity. In the 3 years after RYGB, patients show a progressive weight decline and reach a body weight plateau that is maintained directly and indirectly through peripheral and central mechanisms. Regulation is associated with altered hormonal secretions from the stomach, duodenum, and ileum. Interestingly, in rats, ileal transposition recapitulates RYGB's impact on weight loss and glucose homeostasis without affecting nutrient absorption.[1] Relocation of the ileum increases exposure to nutrients of L cells containing PYY and glucagon-like peptide 1 (GLP-1), implicating these peptides as mediators of weight loss and glucose homeostasis.

Gut–Brain Peptides

RGYB's efficacy is likely explainable by modified secretion of specific gut–brain peptides. Ghrelin and des-acyl ghrelin stimulate appetite and locomoter activity.[2] Ghrelin neurons in the arcuate nucleus synapse onto neuropeptide Y/agouti-related peptide (NPY/AGRP) arcuate neurons and orexin neurons in the lateral hypothalamus.[3] In addition to the anticipated effect of reducing appetite, lowering ghrelin should improve glucose tolerance and insulin sensitivity.[4] Based on reductions in circulating ghrelin levels following RYGB, ghrelin was proposed to be the weight loss mediator.[5–6] However, reports of RYGB–mediated ghrelin lowering are inconsistent. Nevertheless, circulating ghrelin levels do not predict local concentrations in the hypothalamus; therefore, a role for hypothalamic ghrelin cannot necessarily be discounted. Higher production of the satiety peptides cholecystokinin and pancreatic polypeptide inhibit food intake, but RYGB produces a sustained increase of neither cholecystokinin nor pancreatic polypeptide.[7] The most consistent observation following RYGB is exaggerated postprandial increases in the gut peptides PYY and GLP-1.[6–8] PYY_{3-36}, the major circulating form of PYY, acts on the neuropeptide Y Y2 receptor to suppress appetite.[9] Besides inhibiting food intake, both PYY_{3-36} and GLP-1 improve glucose homeostasis.[10]

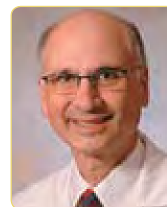
RYGB in Rats and Humans

The diet-induced obese (DIO) rat model provides important insights into the mechanisms regulating weight loss and body weight stabilization after RYGB.[11] Comparisons between DIO rats in which RYGB was successful (RYGB-S), DIO rats in which weight loss was not sustained (RYGB-F), and pair-fed DIO rats support a regulatory role for PYY_{3-36} and GLP-1. The biphasic weight loss response to RYGB in DIO rats mimicked that observed in morbidly obese humans. Reduced caloric intake alone cannot explain RYGB's effectiveness, because both pair-fed and RYGB-F rats regained weight after an initial period of weight loss. Fecal output was greater in RYGB-S rats than in RYGB-F and pair-fed rats. As weight loss reached a plateau, leptin levels stabilized. In RYGB-F and pair-fed rats, low leptin was associated with increased feed efficiency; surprisingly, RYGB-S rats have even lower leptin levels, but they exhibit negative feed efficiency. Hence, despite low leptin, RYGB-S rats, in contrast to the others, fail to compensate for energy insufficiency, implicating involvement of other factors that suppress food intake. Hypothalamic PYY was elevated in RYGB-S rats; similarly, PYY_{3-36} is higher in humans after RYGB. PYY_{3-36} inhibits food intake by suppressing activity of the orexigenic NPY/AGRP neurons in the arcuate nucleus. Consistent with a role for PYY_{3-36}, the ablation of PYY predisposes mice to become obese.[10] The hypothalamic-gut peptide GLP-1 is also elevated selectively in RYGB-S, but not RYGB-F or pair-fed rats. Like PYY_{3-36}, postprandial release of GLP-1 is exaggerated in humans after RYGB, an effect that is sustained for > 36 months.[8] GLP-1 suppresses food intake and is a mediator of leptin action.[12] Indeed, maintenance of weight loss and sustained improvements in glucose tolerance and insulin sensitivity observed in obese subjects following RYGB is perhaps best explained by a combination of increased GLP-1 and PYY_{3-36} and activation of downstream mediators.

To test how gut peptides are involved, researchers conducted a randomized, double-blind study in groups of patients, including those undergoing RYGB. The patients received octreotide to inhibit the release of gut peptides. The RYGB group receiving octreotide experienced an 87% surge in food intake, which strongly suggests that RYGB's benefits are mediated by anorexigenic gut peptides. Because octreotide also inhibits release of the orexigenic gut peptide ghrelin, it is unlikely that ghrelin plays a dominant role in weight loss as a result of RYGB. Collectively, the published experimental results from rodents and humans lead to the conclusion that PYY_{3-36} and GLP-1 are the most important contributors to sustained weight loss after RYGB.

Clinical Researcher Perspective

➤ By John C. Alverdy, M.D., F.A.C.S.



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Highlights

- If bariatric procedures are judged by % excess body weight lost, DS > RYGB > LAGB.
- There is inadequate information to define the precise role of gut hormones in the weight loss response.
- Response to surgery may be a function of both host genes and intestinal microbial genes.
- Understanding the central reward center processing of food in response to the various surgeries is now possible.

The most frequent operations performed for weight loss purposes in the United States include an operation that functions primarily as a mechanical restrictive device, LAGB; a mechanically restrictive and foregut-diverting procedure, RYGB; and a partially mechanically restricting and malabsorptive procedure—pancreatico-biliary bypass with duodenal switch (DS). Each operation elicits weight loss, although in terms of percentage of excess body weight lost, the efficacy runs along the lines of DS > RYGB > LAGB. To identify the mechanism(s) by which weight loss occurs following these operations, most comparisons have been made between LAGB and RYGB. The most striking differences between the anatomy of these two operations is that, when properly completed, LAGB is equally if not more mechanically restrictive than RYGB, and the latter does not cause appreciable malabsorption. Therefore, the observation that weight loss is accelerated with RYGB over LAGB must be explained in terms of either enhanced satiety or increased energy expenditure.

Although numerous reports have demonstrated that the hormones ghrelin, GLP-1, and PYY_{3-36} rise more following RYGB compared with LAGB, in many cases these reports are technically inadequate, involve too few time-point measurements, and are not controlled for environmental noise, sleep disorders, and other co-morbidities. Furthermore, most of these studies were not carried out to late time points (> 2 years) in the course of weight loss, when significant intestinal adaptation occurs.[1] Among experienced bariatric surgeons, it is axiomatic that weight gain, diminished satiety, food cravings, and shifting to other behaviors that activate adjacent central reward centers (e.g., alcohol intake, sex) develop in a significant cohort of patients after bariatric surgery.[2] Meta-analyses of large cohorts of patients demonstrate that weight loss and resolution of co-morbidities is greatest and most durable with DS, followed by RYGB and LAGB. Although levels of potent satiety hormones such as PYY_{3-36} are elevated with DS > RYGB > LAGB, to attribute causality to weight loss remains speculative.

Weighing Up the Hormones

That said, there are compelling reasons to consider a weight loss operation to be the most effective if it results in a hormone signature that most readily controls central processing of satiety and energy expenditure. Although measures (e.g., area under curve and numeric average) of serum markers compared between patients undergoing the various operations make it attractive to conclude that hormone changes regulate success following surgery, essentially no information exists comparing serum hormone markers between successful and non-successful patients who have had the same operation (within-group difference). Unexplored areas of investigation need to be applied to bariatric surgery patients to establish the roles of hormones as energy balance regulators following weight loss operations. Currently available tools must be applied to answer two critical questions regarding hormonal roles in bariatric surgery:

> "... that weight loss is accelerated with RYGB over LAGB must be explained in terms of either enhanced satiety or increased energy expenditure."

1. *How do intestinal flora changes caused by weight loss surgery affect intestinal hormones, plasma hormones, and central processing of satiety signals and energy expenditure?* Numerous landmark reports have now established that the intestinal microbial consortia are key in regulating energy use via both central and peripheral mechanisms.[3] The observation that fecal transfer can express a change in body fat composition, locomotion, and energy balance in animals makes a compelling argument that the intestinal microbiome itself is a contributing factor in obesity.[4] The ability to interrogate the intestinal microbiota composition and function using metagenomics (metabolomics and genomics) has confirmed the long-held suspicion, based on direct culture, that weight-loss surgery profoundly influences the intestinal flora's composition and function.[5] This finding, coupled with numerous reports demonstrating that intestinal flora directly affect gut hormone expression patterns, begs for a more complete understanding of how bariatric surgery shifts energy balance via its intestinal microbiome effects.[6] Thus, interrogating the microbial genome may be as important as checking the host genome to further understanding of how the various operations function to achieve significant, sustainable weight loss.
2. *How are plasma hormone markers processed centrally to affect satiety and energy expenditure?* Whereas plasma hormone profiling may be enormously helpful to a mechanistic understanding of bariatric surgery's success or failure, ultimately it will be important to understand how these hormones are processed centrally to affect not only satiety, but also energy expenditure. Discovering leptin's role in obesity raised excitement about prospective drug therapy, but the unexpected recognition that obese patients have elevated leptin levels led to the conclusion that central hyporesponsiveness to leptin may play a role in obesity. Functional MRI can now be used to determine the relative responsiveness of an individual plasma hormone signature to satiety and energy expenditure, allowing reward center excitation in response to a fixed composition meal to be compared

visually to satiety activation.[7] Understanding these variable responses to different bariatric procedures can then be used to refine their effects or eliminate their use in specific cohorts of patients whose genetic backgrounds or microbial flora render them resistant to surgery. Such studies might help to clarify how agonist–receptor interaction regulates body composition and weight. This appears to be highly dependent on the genetic background of the host, but also on compounds released by the intestinal microbial flora and taken up by the central nervous system.[8]

Clinical Practitioner Perspective

➤ By Manu V. Chakravarthy, M.D., Ph.D.

Dr. Chakravarthy is associate director of clinical research at Merck Research Laboratories, Rahway, N.J.

Highlights

- Bariatric surgery procedures have markedly increased in the past decade, concomitant with decreases in surgical mortality rates.
- Compared with LAGB, RYGB causes greater total body weight loss, more efficient diabetes resolution, hyperlipidemia improvement, and a dramatic decline in diabetes-related deaths.
- RYGB's surgical risk is higher than LAGB, so long-term comparative trials are needed.
- Costs and risks of surgical interventions must be balanced against public health costs of obesity and its complications.

Current Therapeutic Strategies

Traditional approaches of lifestyle interventions (caloric restriction, behavior management, exercise prescriptions) and pharmacological therapies have largely been unsuccessful in combating the obesity pandemic, mainly because the weight loss induced by these interventions is modest and short-lived. Perhaps not surprisingly, surgical approaches to treat severe obesity have rapidly gained favor, especially since the National Institutes of Health established guidelines in 1991 for the surgical therapy of morbid obesity (BMI ≥ 40, or ≥ 35 with co-morbidities), now referred to as bariatric surgery.[4]

The annual frequency of hospital discharges in the United States that included bariatric surgery increased 7-fold between 1996 and 2002,[5] concomitant with decreases in surgical mortality rates.[6] All-cause mortality is also reduced after bariatric surgery, as shown by drops of 30% in the Swedish Obese Subjects Study[7] and of 40% in a retrospective cohort of 7,925 bariatric surgical patients, compared with non-surgical obese patients.[8] Based on these striking findings and other recent clinical trial data,[9] BMI thresholds could possibly be lowered with revised indications for bariatric surgery.

Types of Bariatric Surgical Procedures

Broadly, bariatric procedures are classified as restrictive, malabsorptive, or combined. Purely restrictive procedures such as LAGB reduce the stomach's volume to decrease food intake and induce early satiety. Purely malabsorptive procedures such as biliopancreatic diversion shorten the small intestine to decrease transit time and nutrient absorption. Combined procedures such as the RYGB incorporate both restrictive and malabsorptive elements. The two most common procedures worldwide are LAGB and RYGB, which are primarily performed laparoscopically, thereby significantly curbing perioperative risk and contributing to the rapid spread of obesity surgery.

The LAGB procedure is relatively simple and well standardized. The two available bands—Lapband and Swedish Adjustable Gastric Band—have similar outcomes in postoperative weight loss and complications.[10] Because both bands are adjusted by injecting isotonic liquid into a port, hydraulic bands have potential complications such as port puncture.

By contrast, RYGB procedures are technically more complex. The bypass typically includes a pouch volume of 20–30 ml, an alimentary limb of at least 75 cm, and a biliary limb of at least 50 cm. With the laparoscopic approach, gastrojejunostomy is usually performed with a circular stapler, placing the anvil transgastrically to avoid esophageal injury. The Roux limb is typically placed antecolic and antegastric, and closure of defects in the Roux-limb mesentery and jejuno-jejunostomy mesentery is needed to avoid bowel obstruction.

Bariatric Surgery Risks and Outcomes

RYGB, compared with LAGB, is associated with a greater risk of perioperative complications. These include anastomotic leakage, gastric distension, gastrointestinal bleeds, small-bowel obstruction, and nutritional deficiencies. Recent reports have also highlighted endocrine complications, especially hypoglycemia due to "dumping syndrome" and hyperinsulinemia with nesidioblastosis.[12] Concomitant with these increased complications, patients undergoing RYGB, in contrast to LAGB, had more reduction in total body weight (25% vs. 14%),[7] greater efficacy of diabetes resolution (84% vs. 48%),[11] a decline in hyperlipidemia (95% vs. 71%),[11] and a remarkable 92% plunge in diabetes-related deaths.[7, 8]

Choice of Procedure

Despite the clear procedure-specific differences in disease outcomes, deciding on a specific bariatric procedure must take a tailored rather than one-size-fits-all approach. Furthermore, because RYGB carries increased surgical risk compared to LAGB, long-term comparative trials of these procedures are needed. One approach would be to consider patients' pre-surgery BMI and their co-morbidity status. On balance, patients with more severe obesity (e.g., BMI

> 50 kg/m²) are generally considered good candidates for RYGB or biliopancreatic diversion, whereas LAGB might be more appropriate in milder degrees of obesity. Of course, no single operation is ideal for every morbidly obese patient and all candidates for obesity surgery should receive full disclosure about the various options as well as the risks associated with each.

Summary

With data emerging on the safety and efficacy of bariatric procedures,[6] combined with the limited efficacy of conventional interventions to curb the obesity pandemic, it is time to rethink the current therapeutic approach to obesity and its complications. Costs and risks of surgical interventions must be balanced against the costs and risks of these diseases for public health. For bariatric surgery to become a frontline therapeutic option, knowledge and skills will need to be focused in specialized high-volume bariatric surgery centers, where research and practice can be coordinated to bring about the greatest benefit to patients. ■

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