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Endocrine and metabolic response to gastric bypass

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Abstract

Purpose of review—Diabetes resolves in 80% of individuals undergoing successful Roux-en-Y gastric bypass. Absolute caloric restriction alone resulting from gastric anatomic changes indeed leads to weight loss; however, immediate effects in glycemic control often precede substantial weight loss typically associated with insulin sensitivity. One putative explanation relates to hormonal effects accompanying Roux-en-Y gastric bypass. We reviewed the existing and recent literature to investigate the hormonal changes accompanying Roux-en-Y gastric bypass.

Recent findings—Changes in levels of five candidate enteric hormones have been recently associated with early postoperative glycemic control following Roux-en-Y gastric bypass; the strongest effects are seen with variations in glucagon-like peptide-1, glucose-dependent insulinotropic peptide and ghrelin.

Summary—The unique hybridization of static anatomic restriction and dynamic absorptive bypass lends a duality to the beneficial effects of Roux-en-Y gastric bypass. This duality likely explains the short-term and long-term resolution of diabetes in patients undergoing Roux-en-Y gastric bypass.

Keywords

caloric restriction; gastric bypass; ghrelin; incretin

Introduction

Obesity-related surgical procedures are gaining popularity in the United States. From 16 000 procedures in 1997, there was a 645% increase in the number of bariatric operations performed during 2003 [1]. In 2006, an estimated 177 000 people had bariatric surgery; this number constituted less than 1% of those who met the eligibility criteria. The staggering direct and indirect costs of untreated obesity are on the rise too, estimated to be $117 billion in 2006 [2]. Bariatric surgery is not just associated with long-term weight loss and decreased morbidity and mortality [3,4], but is also expected to exert significant economic impact on obesity; downstream savings are estimated to offset the cost of the surgery within 2–4 years [5•].

Gastric bypass or Roux-en-Y gastric bypass (RYGB), preferred for its safety, accounts for 80–90% of all bariatric procedures [6]. The 30-day postoperative mortality for laparoscopic RYGB may be as low as 0.17% [7•], similar to cholecystectomy (0.12%) [8], although the mortality rates for cholecystectomy in obese individuals can be higher [9•].

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The original description of gastric bypass goes back to 1967 by Mason and Ito [10] on the basis of weight loss observed on patients undergoing partial gastrectomy for ulcer disease. In 1980, Walter Pories introduced and performed modifications to the surgical technique, which represent the current bypass. Initially thought to represent a transient phenomenon, he observed that glycemic control began improving before any significant weight loss occurred [11]. In 1995, he published a 14-year follow-up for 146 RYGB patients with type 2 diabetes mellitus (T2DM) showing a remission rate of 83% [12]. These findings were later confirmed by others with more than 80% remission rate of T2DM [9•,13–15]. Other obesity-related comorbidities, mainly the components of the metabolic syndrome, have undergone parallel improvements in clinical endpoints after RYGB [16•,17,18]. Current intense research efforts are directed at investigating the mechanisms behind such salutary effects of RYGB on T2DM and hypertension. We intend to review the most recent studies exploring the endocrine and metabolic changes accompanying RYGB by performing a literature search using the keyword ‘gastric bypass’. We limited our selection and review process to articles addressing gastrointestinal and systemic hormonal or metabolic changes that could have an impact on energy metabolism and food intake in the context of RYGB.

Roux-en-Y gastric bypass, enteric hormones and metabolism: a real labyrinth (basic considerations)

There exist two anatomic features to RYGB: a restrictive component and a bypass component. The currently adopted surgical procedure as introduced by Pories *et al.* [12] is shown in Fig. 1. It involves the exclusion of a major part of the stomach except for a 20–30-ml pouch created around the gastroesophageal junction with the lesser curvature as its base (this pouch serves as the new food reservoir and defines the restricted segment) and partitioning of the jejunum 40–60 cm from the ligament of Treitz. The distal segment is anastomosed to the gastric pouch establishing oro-anal continuity for food passage. The proximal jejunal segment connects distally through a jejunojejunostomy providing secretory drainage of the bypassed stomach (~90%), duodenum and proximal jejunum. The Roux limb is delineated between the gastrojejunostomy and the jejunojejunostomy. This represents the bypassed section of the RYGB.

The strength of the RYGB lies in the hybridization of restriction and bypass in one procedure. The reduction in intake mediated by restriction is accompanied by dynamic changes in nutrient transport along the gastrointestinal tract. These will result in caloric restriction as well as variable hormonal secretion affecting the intestines and the hormonally active organs along the alimentary tract which constitute the enteroinsular axis, but also the central feedback elements. Thus, resultant changes in hormonal profiles constitute one of the first and most important roles of RYGB.

Ghrelin

Secreted mainly by the gastric fundus and proximal small intestine [19], ghrelin – a powerful orexigenic hormone – stimulates appetite and increases food intake in normal humans [20]. Circulating levels surge with fasting and are suppressed by ingested nutrients. The postprandial suppression is mainly effected by neuronal signals to the intestines and indirectly by food intake through increased insulin levels [21]. In addition to the short-term regulation of appetite and periprandial changes, ghrelin fulfills the criteria of a body weight-regulating hormone. Levels are decreased with high energy intake, that is obese individuals, and increased in lean individuals, during medical weight loss, that is negative energy balance [21] and in anorexia nervosa [22].

The RYGB effects on ghrelin levels are inconsistent among many studies (Table 1); values varied between institutions [15]. The inclusion of recent studies corroborates these disparate findings [23–27,29,30••]. Fasting levels of total ghrelin after RYGB decreased in some studies [24•,25•], increased in few [23,26] and were unchanged in others [27,29,30••]. After RYGB, the postprandial decreases in ghrelin, otherwise seen in normal individuals [21], were blunted [27,28••] in two studies and exaggerated in one [30••].

The assays in most of the reviewed studies (seven out of eight studies) [23-27,29,30••] measured total ghrelin, which includes the active or acylated form as well as the nonactive form. In contrast to active ghrelin, the nonacylated part does not activate the growth hormone secretagogue receptors [31]. The one recent study that measured active ghrelin after RYGB found a decrease in the basal and no change in the postprandial levels in patients studied 4 months after surgery [28••]. Further studies addressing the acylated form of ghrelin would be needed in order to delineate whether a specific and consistent change in secretion is induced or facilitated by RYGB.

Thus far, no consistent pattern of changes in ghrelin levels has been established. The decrease in ghrelin or the lack of increase seen after RYGB stands in contradiction to the usual increase seen in ghrelin with active nonsurgical weight loss. One hypothesis to explain these unexpected findings includes ‘override inhibition‘, as suggested by Cummings and Shannon [32]. An anatomical bypass of the ghrelin-secreting cells in the stomach and duodenum would diminish nutrient contact, simulating a permanent fasting state with continuous ghrelin secretion in the beginning, paradoxically suppressing the usual cyclical variation. This would ultimately result in chronically decreased ghrelin levels [32]. Another putative explanation put forth regarding the disparate findings seen in RYGB patients involves surgical technique. Variation in the size of the gastric pouch (site of the gastric division, i.e. placement of the staple line) or length of the biliopancreatic limb may exclude varying amounts of ghrelin-secreting cells. The anatomic variations could result in direct contact between nutrients and ghrelin-secreting cells remaining either in the stomach or from biliopancreatic limb refluxate. This contact would be expected to maintain the usual cyclic pattern of ghrelin secretion. To help determine whether these hypotheses are valid, a well designed study would include randomization according to surgical technique, preweight and postweight loss evaluation, consistent controls including surgical and diet-induced weight loss.

The incretins: glucagon-like peptide-1 and glucose-dependent insulinotropic peptide

Defined originally in 1979 by Creutzfeldt [33], the incretins are gastrointestinal hormones that stimulate insulin release after enteral nutrition and include glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP).

Glucagon-like peptide-1, secreted mainly by the L-cells in the distal ileum and proximal ascending colon, augments glucose-dependent insulin secretion and inhibits glucagon release by the pancreas [34]. It also slows gastric emptying [35] and enhances central satiety and decreased food intake [36,37]. Its metabolic effects include promoting insulin sensitivity: GLP-1 increases glycogenesis in the liver and skeletal muscle [38]. The direct involvement in glucose metabolism has been coupled with interesting profile changes after RYGB. The postprandial levels of GLP-1 showed significant increase in patients after RYGB [30••,39••,40•,41]. This was seen in the early postoperative period, as low as 1 month after surgery [39••], and chronically as well, more than 4 years after RYGB [41]. These changes were consistent and not seen in comparable individuals when subjected to medically induced equivalent weight loss [39••]. These studies suggest a role for GLP-1 in

mediating early improvements in insulin resistance and eventual resolution of diabetes after RYGB prior to significant weight loss. In the same line of analysis, a paradoxical finding of unclear metabolic or clinical significance has been reported. Glucagon is increased with GLP-1 postprandially following RYGB [39••,41], whereas an increased GLP-1 should physiologically decrease glucagon [34] especially when an improvement in insulin sensitivity is a contemplated outcome.

Glucose-dependent insulinotropic peptide, the second candidate incretin hormone, is stored and secreted by K-cells residing mainly in the proximal gut, that is duodenum and proximal jejunum [42]. There are no clear anatomical distinctions between GLP-1 and GIP-secreting sections along the intestinal tract; colocalization, with immunohistochemical staining using monoclonal antibodies to GLP-1 and GIP, has been described along various parts of the human gut [43]. GIP acts primarily postprandially to increase insulin secretion under hyperglycemic conditions in normal individuals [44]. Whereas GLP-1 continues to stimulate insulin release in type 2 diabetic patients, GIP does so to a much lesser degree [45]. Contrastingly, GIP stimulates lipoprotein lipase activity which may serve to incorporate fatty acids into adipose tissues – a property not shared with GLP-1 [46]. Despite these glycemic and potential lipogenic effects, GIP does not seem to affect satiety or gastric emptying [47].

Recently, Laferrere and colleagues [39••] compared the incretin changes in obese diabetics before and 1 month after RYGB to a control group before and after similar medical weight loss. In the surgical group, they found a higher peak of GIP in the first 45 min after oral glucose intake, but similar values were obtained in both medical and surgical-induced weight loss groups during the entire postprandial period (0–180 min after glucose ingestion). This transient effect did not persist beyond 6–12 months after RYGB [39••]. In a longer follow-up study (27 months), Rodieux and colleagues [30••] found the postprandial spike of GIP to be significantly reduced after RYGB. One putative explanation of the decremental secretion of GIP suggests an association with preferential oxidation of fat accompanied by clearance of triglyceride depots from the liver and muscle [48].

Taken together, RYGB could be inducing earlier and higher peaks of GLP-1, as well as possible attenuated GIP responses. Whereas unlikely the sole mediators of increased insulin sensitivity immediately following RYGB, they likely contribute to resolution of diabetes during the postoperative state.

Peptide YY

Peptide YY (PYY), also known as peptide tyrosine tyrosine, is a 36 amino acid (with amino acids 18 through 36 identical with pancreatic peptide) which originates from the same L-cells secreting GLP-1 along the intestinal mucosa. Its release is stimulated by intraluminal nutrients in addition to hormonal and neuronal inputs [49]. PYY exerts both local and distant effects: it inhibits gastric acid secretion [50] and exocrine pancreatic secretion [51] and delays mouth-to-cecum transit time [50]. An important action of PYY (3-36) is central inhibition of appetite and promotion of weight loss [52,53]. Postprandial PYY response is blunted in obese individuals [53], which may cause a decrease in satiety [54].

Roux-en-Y gastric bypass is associated with an increase in fasting PYY in some studies [26,27,40•], and more importantly a significant rise in the postprandial response of PYY [29,30••,40•]. The exaggerated response observed soon after RYGB could be another candidate to help explain improvements in glucose homeostasis and early weight loss after surgery. These effects may plateau over time: in obese patients followed longitudinally after RYGB, early increases of stimulated PYY release seen 6 weeks after surgery were

maintained but failed to improve further at the 52-week follow-up. However, insulin resistance and body weight continued to decrease significantly in those patients [29].

Pancreatic peptide

Pancreatic peptide is primarily released by the islets of Langerhans in response to proteins and high fat meals [55]. The postprandial increase slows gastric emptying and inhibits further food intake [56]. An important regulator of pancreatic peptide secretion is vagal stimulation of the pancreas [55]. Past studies demonstrated unchanged or decreased levels of pancreatic peptide [57,58] after RYGB. Also recently published, fasting levels of pancreatic peptide has been found to decrease after surgery [59]. On the contrary, a similar profile of fasting and postprandial changes in pancreatic peptide wasobserved in a cross-sectional study evaluating patients post-RYGB, obese and lean controls [40•]. Variations in the surgical approach favoring vagal sparing may preserve cholinergic inputs to the pancreas.

Roux-en-Y gastric bypass and caloric restriction

After gastric bypass, the anatomic restriction to food ingestion is obvious, with limitations on caloric intake. Caloric restriction in obese patients without surgery improves insulin sensitivity and glucose homeostasis significantly before any evidence of weight loss is seen [60]. All types of bariatric surgery include an element of caloric restriction, and this might be the common cause for the associated improvements in insulin sensitivity [61] independent of anatomic changes.

The unique aspect of insulin sensitivity improvements following gastric bypass is its temporal effects. RYGB patients enjoy earlier and higher rates of resolution in T2DM [15]. A recent comparison stimulated glucose kinetics in three groups: two after RYGB or gastric banding and one control. All three groups had similar weights. The postprandial changes in glucose and insulin were found to occur earlier and to a higher extent in the RYGB group compared to the gastric banding and controls. Areas under the curve (AUCs) for glucose were similar among all cohorts. At the same time the insulin rise was higher in the RYGB group, but the total amount of insulin secreted postprandially after RYGB was similar to gastric banding (both higher compared to control) [30••]. Separately, an earlier follow-up post gastric bypass (1 month) in diabetic patients focused on metabolic changes, comparing RYGB patients to a nonsurgical group with similar baseline weights subjected to equivalent amounts of medical weight loss [39••]. Glucose AUC showed a significantly greater decrease in the surgical group; however, a significant decrease in insulin AUC was observed only in the calorically restricted group. Both methods of caloric restriction showed significant and equivalent drops in insulin resistance, measured by the homeostatic model assessment (HOMA) [39••]. These findings in aggregate suggest that RYGB could be associated with an advanced early postprandial response in glucose and insulin secretions, while mediating improved insulin sensitivity and resolution of diabetes similar in magnitude to that associated with caloric restriction alone. Furthermore, these effects may be synergistic with caloric restriction in the postoperative period.

Conclusion

Roux-en-Y gastric bypass has evolved, during the last few decades, from a peptic ulcer disease treatment to the most commonly performed bariatric procedure for surgical weight loss. As technique continues to improve, the favorable effects on the sequelae of obesity and the decreasing complication rate render RYGB a procedure of choice in those who stand to benefit from bariatric surgery. Significant and sustained weight loss is achieved in most instances. Clinical improvements in the comorbidities of obesity, specifically insulin sensitivity and diabetes, are secondary outcomes worth investigating. Their temporal

relationship to the postoperative state suggests intervening endocrine changes that precede the profound weight loss following surgery. These variations are likely stemming from a combined, caloric restriction-intestinal bypass procedure. We highlight the following metabolic and endocrine changes:

1. Although controversy exists among studies, ghrelin is mostly unchanged or decreases after RYGB; medical weight loss usually results in increased ghrelin levels. Bypass of the stomach in RYGB may be linked to changes in ghrelin that are compatible with decreased hunger and food-seeking behaviors. Variations in surgical technique and active ghrelin assay standardization constitute two areas that require further investigation.
2. The delivery of food downstream from the duodenum and proximal jejunum stimulates these segments into early and amplified postprandial response of GLP-1, which in turn stimulates increased insulin secretion and early glycemic control. However, GLP-1 changes do not appear to be the sole mediators, and more work needs to be carried out to determine the independent role of GLP-1 in improving insulin sensitivity in severely obese patients undergoing RYGB.
3. Preliminary studies point to a variable profile of GIP secretion depending on the timing of the testing after RYGB. Longitudinal studies are needed.
4. RYGB reinstates an increase in postprandial PYY, otherwise lost in obese patients. This resurgence may inhibit central appetite and promote weight loss early, with an apparent plateau effect over time.
5. Sparing of vagal input to the pancreas may preserve its capacity to increase postprandial pancreatic peptide and inhibit food intake.
6. Caloric restriction equivalent to the allowed intake after surgery does improve insulin sensitivity long term.

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References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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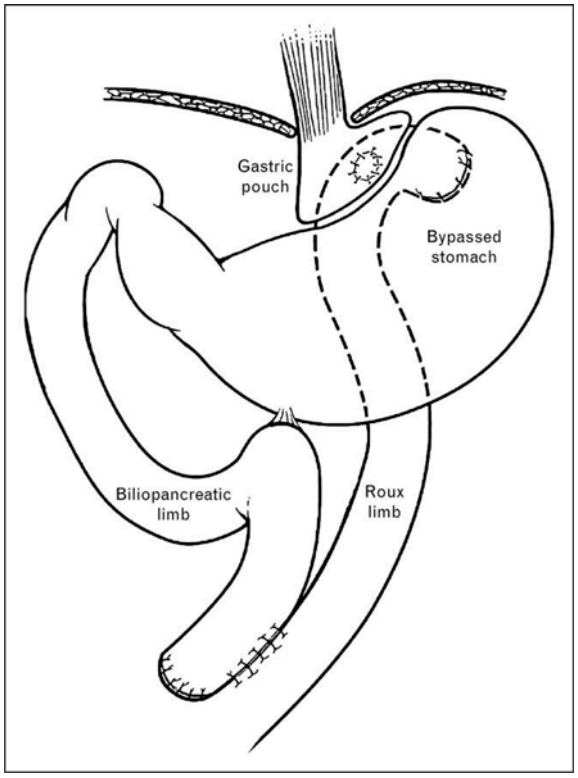

Figure 1. Anatomic rearrangements of the Roux-en-Y gastric bypass

Architecture of the alimentary tract after surgery. A small gastric pouch (20–30 ml) is connected to the jejunum through a gastrojejunostomy establishing oro-anal continuity. The bypassed stomach, duodenum and early jejunum are connected to the Roux limb providing secretory drainage. The Roux limb is delineated between the gastrojejunostomy and jejunojejunostomy.

Table 1

Ghrelin changes after Roux-en-Y gastric bypass

		0–6 months		6–12 months		After 12 months	
Reference	***N***	**Fasting**	**Stimulated**	**Fasting**	**Stimulated**	**Fasting**	**Stimulated**
[23]	34			↑			
[24•]	18					↓	
[25•]	17			↓			
[26]	13			↑			
[27]	6	No change	No change[a]	No change	No change[a]		
[28••]	10	↓	No change[a]				
[29]	25	↓		No change			
[30••]	8					No change	↓[b]

[a]After mixed meal.

[b]After oral glucose.