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Enteroendocrine secretion after roux-en-Y gastric bypass: is it important?

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Abstract

Observational studies suggest that bariatric surgery is the most effective intervention for achieving a significant and durable weight loss. In patients with type 2 diabetes, such surgery is often associated with remission of their diabetes. The mechanism(s) by which surgeries such as Roux-en-Y Gastric Bypass (RYGB) leads to favorable effects on glucose metabolism remain unknown. RYGB is associated with altered secretion of enteroendocrine hormones, leading to the belief that these hormones contribute to the improvement in insulin secretion and action as well as satiation after this procedure. However, it is important to consider the not insignificant effects of caloric restriction and the mechanical changes to the upper gut in determining the outcomes of such surgery.

Keywords

Dipeptidyl Peptidase-4; enteroendocrine secretion; Glucagon-Like Peptide-1; Roux-en-Y Gastric Bypass

Obesity is associated with multiple diseases and comorbidities so that approximately 9% of national healthcare costs have been attributed to excess weight.¹ While behavioral intervention is effective in the short term,² most regain the weight lost within 5 years. Observational studies suggest that bariatric surgery is the most effective intervention for weight loss producing an average weight loss of 30–35% that is maintained in approximately 60% of patients at 5 years.³ This has led to a dramatic increase in the number of procedures performed annually from 13 365 in 1998 to an estimated 102 794 in 2003.⁴ Bariatric surgery is usually considered for patients who have a BMI ≥ 40 Kg M⁻² or a BMI ≥ 35 Kg M⁻² associated with comorbidities such as diabetes.⁵ Roux-en-Y gastric bypass (RYGB) is the most commonly performed bypass procedure and produces gastric restriction together with selective malabsorption. In a meta-analysis of 136 studies of bariatric surgery which included a total of 22 094 patients, Buchwald *et al.* reported that within studies examining type 2 diabetes after bariatric surgery, 1417 of 1846 (76%) patients experienced complete resolution. When categorized by operative procedure, there were clear differences in efficacy. Diabetes resolved in 98.9% of patients undergoing biliopancreatic diversion or duodenal switch. In contrast, the rate was 83.7% for RYGB and 47.9% for adjustable gastric

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AUTHOR CONTRIBUTIONS

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banding.⁶ A retrospective review of 257 patients who underwent the long-limb modification of RYGB (400–500 cm Roux limb length) at our institution reported resolution of type 2 diabetes in 94% of patients.⁷ Consequently, a better understanding of the mechanisms by which bariatric surgery leads to favorable improvements in glucose metabolism and remission of type 2 diabetes, should enable the development of new interventions to treat diabetes.

More recently, two prospective randomized, non-blinded studies concluded that bariatric surgery was superior to medical therapy alone in achieving glycemic control.^{8,9} For example, in the study by Shauer *et al.*, 12% of patients receiving medical therapy achieved an HbA_{1c} < 6.0% in contrast with 42% undergoing RYGB.⁸

What is known about the mechanisms by which bariatric surgery ameliorates glucose metabolism? Rubino *et al.* have suggested a ‘foregut hypothesis’ - that it is bypass of the proximal intestine *per se* that exerts antidiabetic effects.¹⁰ In non-obese diabetic rodents, a stomach-sparing bypass of the duodenum and 20% of the jejunum did not cause weight loss, but improved fasting glucose, insulin action, and oral glucose tolerance.¹¹ This would imply that exposure of the foregut to intraluminal calories leads to elaboration of a diabetogenic mediator. The purported mediator is, at present, unspecified and unidentified. An alternative hypothesis – the ‘hindgut hypothesis’ – has suggested that the increased delivery of calories to the jejunum/ileum increases enteroendocrine secretion, most notably that of Glucagon-Like Peptide-1 (GLP-1), which consequently leads to improved insulin secretion and myriad other beneficial effects on glucose metabolism.¹² High concentrations of GLP-1 are commonly encountered in the immediate postprandial period in patients with upper gastrointestinal surgery including gastric bypass surgery.

In this issue of *Neurogastroenterology & Motility*, Mumphrey *et al.* sought to examine the changes in enteroendocrine cell numbers and function in a rat model of RYGB, using an experimental design with appropriate control experiments.¹³ The operated animals exhibited weight and fat mass loss as well as an improvement in glucose tolerance. This was accompanied by an increase in GLP-1, PYY, and amylin concentrations similar to that observed in humans after RYGB. The gut hyperplasia and hypertrophy observed in animals undergoing RYGB were compared with animals that underwent sham operation – with care being taken to ensure an identical amount of surgical trauma in these animals. The authors comprehensively assessed the absolute numbers and subsequently the density of cells expressing CCK, GLP-1, 5-HT, and Ghrelin.

They observed an increase in the surface area and diameter of the Roux and common limbs, but not of the biliopancreatic limb. This was accompanied by hypertrophy of the longitudinal and circular muscle layers. While the numbers of enteroendocrine cells increased overall, when expressed as a function of intestinal cross-sectional area, overall densities were unchanged – with the exception of neurotensin-immunoreactive cells which exhibited a slight decrease – and cells staining for CCK which exhibited an increase in density in the common, but not the Roux, limb. What is the significance of these findings? The experimental design could not examine the mechanisms underlying the effect of RYGB on enteroendocrine secretion such as whether regulation of secretion or secretory efficiency is altered. Unfortunately, at present, enteroendocrine secretion can only be measured qualitatively using circulating hormone concentrations which represent the net sum of secretion and clearance.¹⁴ Moreover, the glucose-sensing ability of L-cells (the source of GLP-1 and PYY), can explain the alteration in secretion of these hormones in response to increased intraluminal caloric content.^{15,16}

Bariatric surgery is associated with a rapid improvement in fasting glucose concentrations and in insulin action (at least as measured using qualitative methodology). However, these changes are also observed in response to significant caloric restriction (600–800 Kcal daily), suggesting that these changes are not unique to bariatric surgery.^{17,18} These changes occur early in the postoperative course and independently of a significant change in weight.¹⁹ Therefore, caloric restriction *per se* likely plays an important part in the favorable metabolic changes observed after bariatric surgery.

Glucagon-Like Peptide-1 increases insulin secretion in a glucose-dependent manner and is secreted in response to meal ingestion. In pharmacological concentrations, GLP-1 also suppresses glucagon secretion, delays gastric emptying, and decreases appetite. However, GLP-1 has no metabolic effects independent of its actions on insulin and glucagon secretion and therefore cannot explain effects of bariatric surgery on glucose metabolism prior to weight loss.²⁰ Moreover, GLP-1 is rapidly degraded to its inactive metabolite by Dipeptidyl Peptidase-4 (DPP-4) which mediates removal of the two *N*-terminal amino acids necessary for activation of its cognate receptor. Certainly, defects in GLP-1 secretion do not seem to play a role in the pathogenesis of type 2 diabetes and it is still uncertain if changes in GLP-1 secretion contribute significantly to the changes in glucose metabolism after bariatric surgery.¹⁴

Could enteroendocrine secretion after bariatric surgery explain the changes in satiety observed after bypass surgery? While uncertainties abound in this regard, especially given the rapid degradation of active GLP-1 by DPP-4 (although PYY is activated by this enzyme), it would certainly be important not to overlook the restrictive aspects of bariatric surgery which introduce a significant mechanical restriction to the amount of food that can be ingested at a given time. In such circumstances it is worth observing that sleeve gastrectomy (which does not appear to alter enteroendocrine secretion) seems to have similar effects to RYGB on glucose metabolism despite a lesser effect on weight loss.⁸ It remains to be ascertained whether the differences in long-term weight loss are a reflection of the malabsorption component of RYGB *vs* an effect of circulating enteroendocrine hormones which promote satiation.

In summary, while RYGB is associated with changes in enteroendocrine secretion that may explain some of the changes in metabolism and satiety occurring after intervention, it is important to remember the effects of caloric restriction *per se*, as well as the mechanical effects of surgery may be as important in determining outcomes after surgery. As such, the study by Mumphrey *et al.* is important in that it demonstrates that while absolute enteroendocrine cell numbers increase, they increase in concert with the increase in numbers of other intestinal cells. Such changes likely are a reflection of the altered nutrient delivery after RYGB. Whether these cells contribute significantly to metabolic effects of bariatric surgery requires further study.

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