

MECHANISMS OF IMPROVED GLYCEMIC CONTROL FOR TYPE 2 DIABETES PATIENTS AFTER BYPASS SURGERY BEYOND THE WEIGHT LOSS

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Behavioral and pharmacological intervention to treat obesity and obesity-associated comorbidities, in specially diabetes, usually results in only 5-10% weight loss. Bariatric surgery provides substantial and sustained weight loss, with some surgeries resulting in 30% weight loss. Moreover, these surgeries seem to have metabolic effects that are independent of weight loss, and understanding these additional effects could provide insights into the pathogenesis of type 2 diabetes mellitus and assist in development of new procedure, device and drugs both for obese and non-obese diabetes patients. The mechanisms behind the amelioration in metabolic abnormalities are largely unknown but may be due to change in energy metabolism, gut peptides and food preference. This review summarizes current knowledge on the effects of bypass bariatric procedure on remission/resolution type 2 diabetes mellitus.

Key words: bypass bariatric surgery, type 2 diabetes, weight loss, gut hormones.

INTRODUCTION

Obesity and its associated type 2 diabetes mellitus (T2DM) are an ongoing health-care problem worldwide^{1,2}. Moreover, both diseases are closely related and difficult to control by the conventional medical treatment, including diet, pharmacological therapies and behavioral modification³⁻⁵. Bariatric surgery is the most effective treatment for obesity, and there is powerful evidence that this procedure can cure most of the associated T2DM in patients with morbid obesity⁶⁻¹⁰. Current consensus for bariatric surgery (International Diabetes Federation–2011) is set at body mass index (BMI) >35 kg/m² or >40 kg/m² with diabetes and other comorbidities not controlled by optimum medical treatment. Although weight loss undoubtedly plays an important long-term role in improving glycemia

after bariatric surgery, several findings are consistent with additional weight-independent antidiabetes effect of this operation. In this context, “metabolic” surgery recently has been proposed as a new treatment modality for obesity-related T2DM for patients with BMI <35 kg/m²^{11,12}.

This type of surgery is divided into three categories: restrictive, malabsorptive and hybrid procedures, the later combining gastric restriction and malabsorption. Roux-en-Y bypass surgery (RYGB) is a hybrid procedure, comprising about 70% to 75% of all bariatric procedures. In RYGB the stomach is divided in two parts and the small bowel is divided and rearranged into a Y-configuration; nutrients pass from the small upper stomach pouch (~20–30 ml) to the jejunum via a “Roux limb” and the bowel continuity is restored by an entero-entero anastomosis, at which site the excluded biliary limb meets the alimentary limb (show the Figure 1).

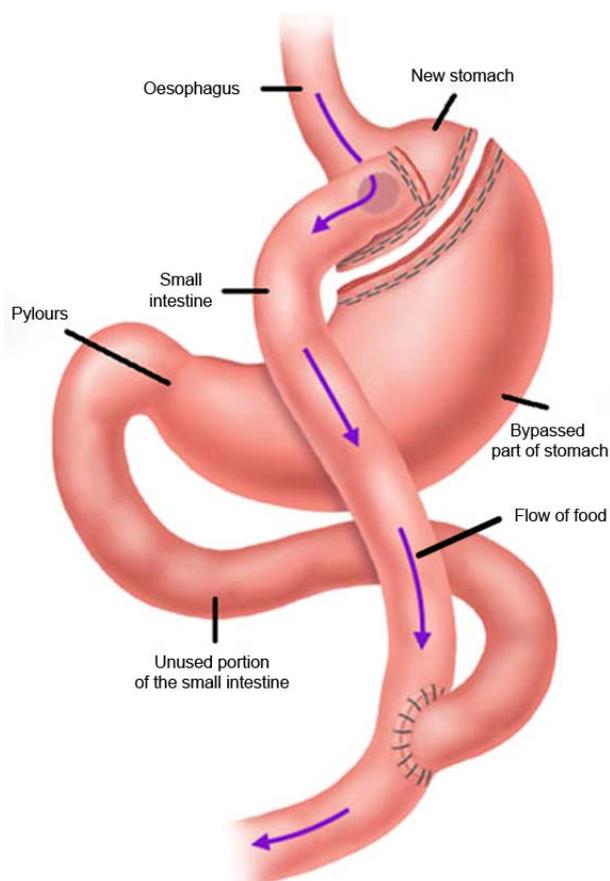


Fig. 1. The gastrointestinal anatomy after Roux-en-Y gastric bypass.

PROPOSED MECHANISMS FOR IMPROVED GLUCOSE METABOLISM AFTER BYPASS SURGERY

In 1995 Pories *et al.*⁶ reported that among 146 severely obese patients with T2DM who suffer gastric bypass, 121 (respectively 83%) experienced a rapid and prolonged postoperative normalization of plasma glucose levels without the need for glucose-lowering medication. This observation was later replicated in several studies and confirmed in a large meta-analysis of 621 studies, which reported that diabetes remission was seen in approximately 81% after RYGB⁹. Trials in people with BMI < 35 kg/m² have reported complete remission of T2DM in a similar or even greater percentage of cases as in severely obese patients undergoing RYGB^{11,13}.

There are several plausible hypotheses by which RYGB procedure improve T2DM independently by weight loss. None of these theories is necessarily exclusive of these others, and any or all them may be operational to some degree.

Ghrelin responses to RYGB

Ghrelin was discovered in 1999 and it is a 28 amino acid peptide that is the natural ligand for the growth hormone secretagogue (GHS) receptor^{14,15}. Based on its structure, it is a member of the motilin family of peptides. When administered peripherally or into the central nervous system, ghrelin stimulates secretion of growth hormone, increases food intake, and produces weight gain^{16,17}. In lean individuals, fasting plasma ghrelin levels are approximately 550 to 650 pg/mL. Circulating ghrelin levels are low in obesity (in the range of 200 to 350 pg/mL) and states of positive energy balance, and are inversely correlated with body mass index (BMI)^{18,19}.

Ghrelin is produced more than 90% by the stomach and duodenum tissue into enteroendocrine cells. In this context, ghrelin regulation might be disturbed following RYGB. Indeed, two clinical studies provided the first evidence that 24-h period profiles and fasting levels of ghrelin were extremely reduced after RYGB^{20,21}, a paradoxical response in the face of profound prior weight loss. Other studies found no significant change in human ghrelin levels after RYGB. Ghrelin is produced primarily in the stomach, where the enzyme agrelin-O-acyl transferase activates ghrelin by acylating a side chain. Ghrelin is found in the circulation in both acylated and desacylated forms; in most of studies, total ghrelin rather than active ghrelin, was measured. Thus, the reason for the discrepancies may well be due to the poor sensitivity of the techniques that are widely available to evaluate ghrelin²².

Beyond contributing to the marked decrease in appetite and food intake post bypass gastric surgery, low ghrelin secretion might also help improve glucose tolerance²³. This peptide in normal state has four other actions: it blocks intracellular insulin signaling directly in hepatic cells, stimulates secretion of insulin counterregulatory hormones, suppresses the insulin-sensitizing hormone adiponectin and inhibits insulin secretion^{23,24}. All of these actions to raise blood glucose levels are blocked by RYGB by reduction of the ghrelin secretion.

The lower intestinal hypothesis (hindgut hypothesis)

This hypothesis postulates that bypass bariatric surgery create intestinal shortcuts to expedite

delivery of ingested nutrients to the lower bowel accentuate the secretion of glucagon-like peptide-1 (GLP-1), thereby improving glucose metabolism.

GLP-1 is an incretin produced primarily in the ileum and colon by L-cells (in response to enteral nutrient intake), which also secrete peptide YY (PYY) and oxyntomodulin^{25,26}. All three of these peptides reduce food intake and the mechanisms implicated are slowing gastric emptying and inhibition of gastric acid secretion.

GLP-1 and PYY are secreted within 15-30 minutes after food intake^{27,28}. Moreover, GLP-1 secretion in normal state arises not only from direct nutrient contact with distal intestinal L-cells, but also from proximal nutrient-related signals that are transmitted from the duodenum to the distal bowel via neural pathways. As the latter mechanism is silenced after RYGB, this procedure might theoretically lower postprandial GLP-1 levels. But, higher GLP-1 and PYY levels have been reported in post RYGB patients compared with pre RYGB²⁹⁻³³. Consistent with elevated postprandial GLP-1 secretion³⁴⁻³⁹, post RYGB patients have an increased incretin effect^{32,40}. GLP-1 not only enhances insulin secretion but can also increase proliferation and decrease apoptosis of beta-cells²⁶. Thus, GLP-1 is a candidate mediator of the increase in beta-cells mass and it is responsible by post RYGB hyperinsulinemic hypoglycemia^{41,42}.

In addition to regulating appetite and body weight, PYY exerts glucoregulatory properties. In rodent studies it showed that PYY-36 (the predominant circulating form) enhances insulin-induced glucose disposal independently of food intake and body weight⁴³. Thus, elevated levels of PYY after RYGB could contribute to the improved glucose homeostasis.

The upper intestinal hypothesis (foregut hypothesis)

This hypothesis postulates that exclusion of a short segment of proximal small intestine from contact with ingested nutrients exerts direct anti-diabetic effects, possibly due down-regulating unidentified anti-incretin factor(s). Francesco Rubino developed a gastric-sparing variant of RYGB, called duodenal-jejunal bypass (DJB), in which the stomach is left intact, but an intestinal bypass is created that excludes from digestive continuity the segment of proximal small intestine⁴⁴. In obese and non-obese model rats of

polygenic T2DM, DJB improved rapidly and durably diabetes, even though it caused no reduction in food intake and body weight compared with sham-operated controls^{44,45}. Several small human studies of DJB all show benefits in glycemic control, including among non-obese patients, with little or no weight loss.

An unexpected feature of DJB is that it reduces fasting and postprandial blood glucose levels to approximately the same degree with a major impact on Hb1c levels⁴⁶⁻⁴⁸.

Glucose-dependent insulintropic polypeptide (GIP) is another endocrine insulintropic factor, released by the K-type endocrine cells, located in the proximal gut⁴⁹. This factor has some metabolic roles: control of glucose-dependent insulin and postprandial glucagon levels and fatty acid metabolism⁵⁰. Some data had shown decreased levels of GIP in patients after RYGB and a reduction in β -cell stimulation/insulin release. Thus, it can be suggested that this mechanism can contribute to the early resolution of diabetes^{50,51}.

All these data support the role of proximal intestine exclusion as a new fundamental physiological effect of RYGB.

Bile acids alteration

Change in bile acids may also be a link between nutrient sensing and gut hormone change and/or mechanism for the benefits of bypass surgery. Bile acids are fat solubilizers, but have also been found to activate nuclear transcription factors that regulate genes involved in lipid and glucose metabolism in the liver and brain⁵². It has also been shown that bile acids can activate TGR5, a G-protein-coupled receptor, and that TGR5 activation regulates GLP-1 secretion⁵³.

Bile acids have been found to be twofold increased in humans after RYGB, in a study comparing non-diabetic post RYGB patients with morbidly obese and overweight controls^{54,55}.

Moreover, bile acid concentrations were correlated with important metabolic variables, such as inverse relationships with 2 hours post-meal glucose and triacylglycerols, while correlations with adiponectin and peak postprandial GLP-1 concentration were positive⁵⁵.

Thus, change in bile acids may be a key mediator of change in glucose and energy homeostasis with bypass surgery.

CONCLUSIONS AND FUTURE PROSPECTS

Weight loss and resolution of T2DM after RYGB appear to be the composite outcome of multiple contributing mechanisms. RYGB is associated with metabolic improvements that are distinct from those that are caused by weight loss alone. Current evidence suggests that the key mechanism behind the weight loss and metabolic beneficial effects is increased hindgut stimulation due to enhanced nutrient delivery and subsequent excessive release of hindgut hormones, such as GLP-1 and PYY.

Thus, RYGB is a promising treatment for inadequately controlled obesity-related T2DM patients. Future studies in the RYGB area have the potential to discover new drug targets for the treatment of type 2 diabetes.

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