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Review

Intestinal peptide changes after bariatric and minimally invasive surgery: Relation to diabetes remission

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ABSTRACT

Bariatric surgery is very effective in achieving and maintaining weight loss but it is also associated with improvement of obesity metabolic complications, primarily type 2 diabetes (T2D). Remission of T2D or at least a net improvement of glycemic control persists for at least 5 years. The bypass of duodenum and of the first portion of the jejunum up to the Treitz ligament as in Roux-en-Y Gastric Bypass (RYGB), or the bypass of the duodenum, the entire jejunum and the first tract of the ileum, such as in Bilio-Pancreatic Diversion (BPD), achieve different results on insulin sensitivity. Insulin resistance is the major driver of T2D manifesting long before insulin secretion failure. In fact, T2D development can be prevented by treatment with insulin sensitizing agents. Interestingly, RYGB improves hepatic insulin sensitivity while BPD ameliorates whole-body insulin sensitivity.

Two major theories have been advocated to explain the early remission of T2D following RYGB or BPD before a meaningful weight loss takes place, the foregut and the hindgut hypotheses. The former holds that the bypass of the proximal intestine, i.e. duodenum and jejunum, prevents the secretion of signals − including nervous transmitters and hormones − promoting insulin resistance, the latter instead states that the delivery of nutrients directly into the ileum stimulates the secretion of hormones improving glucose disposal. The most studied candidate is Glucagon Like Peptide 1 (GLP1). However, while there is unambiguous evidence that GLP-1 stimulates insulin secretion, its direct action in lowering insulin resistance, independently of the effect on weight loss secondary to its satiety action, is utterly controversial.

In this review we examine the effects on T2D and gastrointestinal peptide secretion produced by different types of metabolic surgery and by minimally invasive endoscopic surgery, whose utilization for the treatment of obesity and T2D is gaining wider interest and acceptance.

1. Introduction

Contrary to lifestyle modifications that are associated with an average reduction of 1.56 kg in weight loss regain at 1 year as compared with controls and no significant changes at 5 years [1], bariatric surgery is very effective in maintaining weight loss, with a mean difference of −26 kg (95% confidence interval −31 to −21), $P < 0.001$) from the baseline weight at 2 years as compared with individuals undergone non-surgical treatment [2]. Meta-analysis of bariatric randomized and prospective trials at 5 years report changes only on body mass index (BMI) with a BMI reduction of 11.40–14.32 kg/m^2 [3]; early (≤30 days) mortality rate 0.08%, > 30 days mortality rate 0.31%; complication rate 17% and reoperation rate of 7%.

The weight loss associated with certain types of bariatric surgery, such as Roux-en-Y Gastric Bypass (RYGB) and Sleeve Gastrectomy (SG), has been shown to be due to a reduced food intake consequent to both a smaller gastric volume and changes in gastrointestinal peptide secretion. The energy intake is reduced, in fact, to 47–66% at 6 months and to 19–49% at 2–3 years [4–7].

In contrast, nutrients, and in particular fat malabsorption accounts for the weight loss observed after Bilio-Pancreatic Diversion (BPD), where the size of the gastric remnant is at least 15 times larger than the gastric pouch of RYGB.

RYGB, BPD and, likely, SG cause diabetes remission or, at least, a net improvement of glycemic control that seem to be independent of weight loss and for this reason the term metabolic surgery was envisaged [8].

Insulin resistance is the major driver of type 2 diabetes (T2D) manifesting long before insulin secretion failure [9]. In fact, T2D development can be prevented or deferred by treatment with insulin

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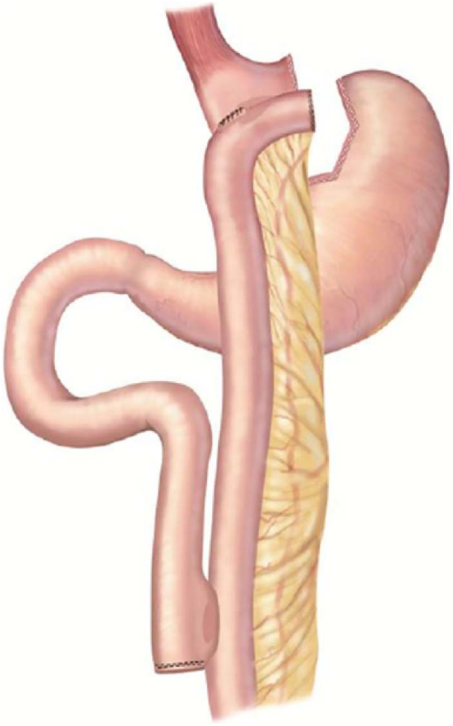

Fig. 1. Roux-en-Y Gastric Bypass.
From Mingrone G, Panunzi S, De Gaetano A, Guidone C, Iaconelli A, Leccesi L, Nanni G, Pomp A, Castagneto M, Ghirlanda G, Rubino F. Bariatric surgery versus conventional medical therapy for type 2 diabetes. N Engl J Med. 2012 Apr 26; 366 (17):1577–1585. Copyright © (2017) Massachusetts Medical Society. Reprinted with permission

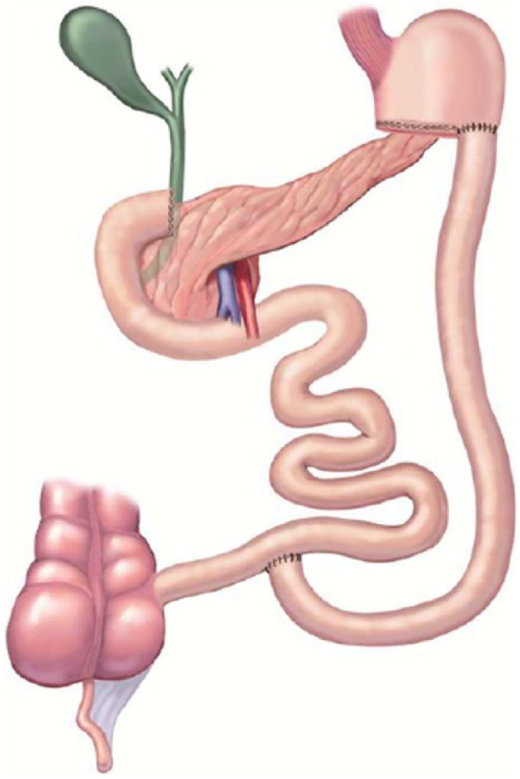

Fig. 2. Bilio-Pancreatic Diversion.
From Mingrone G, Panunzi S, De Gaetano A, Guidone C, Iaconelli A, Leccesi L, Nanni G, Pomp A, Castagneto M, Ghirlanda G, Rubino F. Bariatric surgery versus conventional medical therapy for type 2 diabetes. N Engl J Med. 2012 Apr 26; 366 (17):1577-1585. Copyright © (2017) Massachusetts Medical Society. Reprinted with permission

sensitizing agents [10].

The bypass of the duodenum and of the whole jejunum, like in BPD, rapidly restores whole-body insulin sensitivity [11] while the bypass of the duodenum and the first portion of the jejunum up to the Treitz ligament, such as in RYGB, improves hepatic insulin resistance early before any significant weight loss takes place [12].

Searching in PubMed for “bariatric surgery or metabolic surgery and diabetes remission” retrieves 814 publications, 637 of them in the last 5 years, meaning that there is a great deal of attention of the scientific community on this issue.

However, until now there is no clear evidence of the mechanisms inducing diabetes remission and/or insulin resistance improvement after metabolic surgery.

2. Laparoscopic metabolic surgery

2.1. Major types of bariatric operations

2.1.1. Roux-en-Y gastric bypass

This operation (Fig. 1), performed laparoscopically, includes transection, with linear surgical staplers, of the stomach just below the cardia in such a way as to create an upper pouch of 25–30 ml based on the lesser curvature. The remaining stomach is left in place and is excluded from food transit. Next the jejunum is divided at about 50 cm from the duodenal-jejunal- junction (ligament of Treitz): its distal end is anatomized to the proximal gastric pouch while its proximal end is connected to the jejunum some 70–150 cm distal to gastric anastomosis.

2.1.2. Bilio-pancreatic diversion/duodenal switch

The original BPD operation (Fig. 2) envisages a distal gastrectomy leaving a gastric pouch of 400 ml or more and with closure of the duodenal stump. The ileum is then transected at 2.5 m from the ileo-cecal valve: its distal end is brought up and anastomized to the remaining stomach making up the so called alimentary tract. The proximal end of the divided jejunum, which carries the bile and the pancreatic juice (bilio-pancreatic tract), is connected to the alimentary tract at about 50 cm from the ileo-cecal valve. A well known variant of BPD is the duodenal switch procedure that differs from the above described operation mainly in the type of gastric resection, which is vertical instead of horizontal, very much alike what is done for SG.

2.1.3. Sleeve gastrectomy

SG (Fig. 3) is performed through the laparoscopic approach. This procedure consists essentially of a vertical partial gastric resection: the stomach is resected with repeated applications of surgical staplers along the greater curvature from a point just proximal to the pylorus up to the

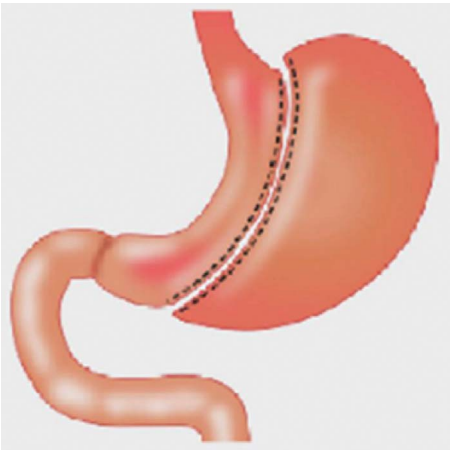

Fig. 3. Sleeve Gastrectomy.