

UPDATE ON THE MECHANISMS FACILITATING WEIGHT LOSS AND RESOLUTION OF TYPE 2 DIABETES FOLLOWING BARIATRIC SURGERY

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Abstract

The prevalence of type 2 diabetes mellitus (T2DM) and obesity is steadily increasing worldwide. To fight the twin pandemics of obesity and T2DM, clinicians need every tool they can get. Major, durable weight loss is uncommon with medical and behavioral approaches; many diabetes drugs promote weight gain, while using them to obtain better blood glucose profiles increases the risk of hypoglycemia. Bariatric surgery seems to be the most effective method for promoting major and durable weight loss in obese subjects, leading also to ameliorations of obesity-associated co-morbidities, especially T2DM. Currently, indications for bariatric surgery include morbidly obese patients or patients with a body mass index (BMI) >35 with significant co-morbidities. Currently, bariatric surgery (also referred to as “metabolic surgery”) is advocated for the treatment of T2DM even in overweight subjects who do not meet the current BMI criteria. This review examines the current evidence regarding the mechanisms of T2DM resolution following bariatric surgery.

key words: bariatric surgery, type 2 diabetes, obesity, weight loss

Introduction

The prevalence of type 2 diabetes (T2DM) is rising in parallel with that of overweight and obesity, driven by several interactions with an “obesity-prone” environment (high-energy diets, reduced physical activity, etc.) [1]. In 2011, an estimated 366 million people had diabetes, and this number is predicted to rise to 522 million by 2030 [2]. Thus, prevention

and treatment of the combination of T2DM and obesity are important public health priorities.

As we know, T2DM is both a heterogeneous and progressive disease. To expect it to be fully controlled by lifestyle and pharmacological treatments is unrealistic [3,4]. Classical used drugs, such as sulphonylureas and metformin, and newer ones such as thiazolidindiones, dipeptidyl

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peptidase 4 inhibitors and glucagon-like peptide 1 (GLP-1) agonists, are useful but do not provide adequate control in many cases [3,5]. Insulin, while ensuring an excellent metabolic control if correctly used, associates the risk of hypoglycemia and weight gain.

Therefore, new treatments are needed to sustain glycemic control, reverse or delay the decline of beta-cell function, assist weight loss and improve insulin action, in the same time avoiding hypoglycemia, and exerting a favorable effect on cardiovascular risk.

Bariatric surgery, a form of gastrointestinal surgery that was initially designed to achieve and sustain substantial weight loss, proved to be an appropriate intervention to prevent and treat T2DM [6]. This type of surgery is divided into three categories: restrictive, malabsorptive and hybrid procedures, the later combining gastric restriction and malabsorption. For example, vertical banded gastroplasty (VGB) is a restrictive procedure, where a band and staples are used to create a small stomach pouch; in the bottom of the pouch, there is a 1 cm opening through which the stomach contents can flow to the rest of the gastrointestinal tract (GI). Roux-en-Y bypass surgery (RYGB) is a hybrid procedure, where 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 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.

The evidence that bariatric surgery improves glycemic control in morbidly obese patients with T2DM was initially reported more than 50 years ago [7]. In 1995 Pories et

al. [8] described sustained changes in glycemic control for up to 14 years after gastric bypass surgery in severely obese T2DM subjects. They reported that 82.9% patients with T2DM and 98.7% patients with glucose impairment maintained normal levels of plasma glucose, HbA1c and fasting insulinemia after bypass gastric surgery. Subsequent retrospective studies have confirmed these findings.

The implementation of laparoscopic, minimally invasive techniques, followed by marked reductions in morbidity and mortality increased the interest for these methods and led to a Diabetes Surgery Summit of experts in Rome in 2007, the inclusion by the American Diabetes Association of bariatric surgery as a treatment option for diabetes in 2009 and an International Diabetes Federation position statement in 2011 [9-11].

Mechanisms for improved glycemic control after bariatric surgery

Although weight loss has a role in improvement of diabetes following surgery, other mechanisms also seem to be implicated and are still under investigation [12]. The non-weight loss effects of bariatric surgery like reduction in hepatic insulin resistance and improved insulin secretion, raised interest in surgery as a treatment for T2DM patients with BMI in the overweight range.

There is increasing evidence for a role of two presumed mechanisms for the change in glucose metabolism and insulin resistance following bariatric surgery:

1. Short-term improvements in glucose metabolism and insulin resistance are caused by caloric restriction, being modulated by the entero-insular axis

2. Long-term improvements in glucose metabolism and insulin resistance are due to decreases in fat mass and mediated through changes in adipocytokines.

Reduced food intake

In 1991, Deitel et al. observed that T2DM improved after VGB in patients before substantial weight loss had occurred [13]. They concluded that this clinical improvement in T2DM correlated with the decrease in caloric intake of these patients. Although *malabsorption* is a frequently cited mechanism for postoperative weight loss following surgical bypass [13], malabsorptive states result in reduced circulating levels of albumin and pro-albumin, and increased fecal fat excretion (rarely encountered in bariatric surgery) and are not the major cause of weight loss.

Gastric volume reduction, due to reduced stomach size and removal of the highly distensible gastric fundus following different surgery procedures, increases gastric pressure and results in early satiety and smaller meal consumption [14]. In response to reduced caloric intake, homeostatic mechanisms that usually maintained body weight would be anticipated to induce a compensatory increased intake of calories-dense food and/or increased meal frequency, thus limiting weight loss. This is not valid in the case of RYGB since patients report reduced appetite, consume fewer meals and decrease their intake of energy-dense foods [15,16]. In comparison, the VGB, an operation with a similar degree of gastric restriction, is associated with less consistent appetite reduction and increased consumption of high energy foods [15,16].

The role of gut hormones. Another aspect of the reversal of diabetes mellitus observed after bariatric surgery is the rapidity of its appearance, T2DM remission occurring within days after operation, before major weight loss appeared. Thus, the rapid resolution of T2DM cannot be explained by weight loss alone, and there is increasing evidence that alterations in circulating gut hormone levels induced by bariatric surgery play a key role in mediating both the altered eating behavior and improved glucose homeostasis.

The concept behind this theory is that rerouting of food through an anatomically altered and/or shortened gastrointestinal tract results in increased delivery of incompletely digested nutrients to the distal gut, over stimulating the specialized L-cells. These cells release gut hormones such as the incretin glucagon-like-peptide (GLP-1) and peptide YY (PYY), both of which exert anorectic actions. Supplementary, GLP-1 stimulates insulin secretion in response to nutrient ingestion and inhibits glucagon secretion, gastric acid secretion, hepatic glucose production. Its actions are mediated by GLP-1 receptors expressed both in peripheral tissues and central nervous system (CNS) [17-22].

PYY has numerous roles in the GI: it increases ileal fluid and electrolyte absorption, it attenuates gallbladder contraction and slows gastric emptying, enhances insulin-induced glucose disposal, independently of its effects on food intake and body weight [23].

Postprandial GLP-1 and PYY levels are potently increased after VGB and RYGB [24,25].

Gastric inhibitory polypeptide (GIP) is also an incretin hormone produced by the K-cells located in mucosa of duodenum and jejunum,

and has several metabolic roles: control of glucose-dependent insulin and postprandial glucagon levels and fatty acid metabolism [22]. Some data have shown decreased levels of GIP in patients after by-passing the duodenum/proximal jejunum (eg. RYGB) and a reduction in β -cell stimulation/insulin release. Thus, it can be hypothesized that this mechanism is responsible for the early resolution of diabetes [22,24,26].

Cholecystokinin (CCK), a classic satiety hormone, is responsible for modulating hunger in response to meals [27,28]. Thus, in response to a meal, CCK is released rapidly into the circulation from the duodenum and jejunum, fat and protein- rich meals being particularly potent stimuli for its release. CCK is also released in response to gastric distension [29,30]. This hormone action is on CCK-receptors on vagal afferents [31].

Gastrectomy obtained by different surgical procedures increases CCK release, it reduces food intake and promotes weight loss.

Ghrelin, is a unique orexigenic hormone, released from the P/D1 cells located in the fundus of the stomach in response to nutrient ingestion [32,33]. With receptors in the arcuate nucleus and the lateral hypothalamus, ghrelin stimulates the hypothalamic release of various neuropeptides such as neuropeptide Y (NPY) a growth hormone (GH) and thus it facilitates an orexigenic state [32-35]. This hormone also exerts “prodiabetic” properties: it stimulates insulin counter-regulatory hormones, suppresses the insulin-sensitizing hormone adiponectin, blocks hepatic insulin signaling and inhibits insulin secretion. Several studies have assessed the impact of bariatric surgery on circulating ghrelin profiles and shown that overall energy balance might

be a more important determinant for postsurgical circulating ghrelin levels [34-38]. Hence, reduced ghrelin secretion after bariatric surgery involving gastric resection (and concomitant vagotomy) could contribute to postoperative improvement in glucose homeostasis.

Bile acids. Besides to emulsifying fat in the lumen, bile acids enter circulation and interact with specific receptors on various tissues that activate some nuclear transcription factors which regulate genes involved in cholesterol and glucose metabolism in the brain and liver [39,40]. There is also evidence about the role of bile acids in regulating GLP-1 secretion. Several studies showed increase of circulating bile acids after VGB and RYGB through increased proximal re-absorption and decreased excretion [41]. Thus, change in bile acids may be an important mediator of changes in GLP-1 and glucose homeostasis induced by bariatric surgery.

Change in food preferences. A shift from high-glycemic index, high-fat foods to low-glycemic-index, low-fat foods is beneficial for people with T2DM [42-44]. All bariatric surgery procedures change food choices: biliopancreatic diversion-duodenal switch reduces fat intake, gastric banding usually limits consumption of breads and pasta while gastric bypass reduces intake of sweet and fatty foods.

Decrease in fat mass. Central obesity is a powerful risk factor for the development of insulin resistance. The significant changes in waist circumference (a surrogate marker of central adiposity) caused by bariatric surgery may indicate great improvements of central obesity. Adipose tissue is known to express and secrete a variety of adipocytokines that

have been involved in the development of insulin resistance and atherosclerosis.

Released by the adipose tissue, *leptin* acts on the hypothalamus to counteract the orexigenic signals induced by ghrelin and NPY, as shown in [Figure 1](#). In addition, leptin also blocks anandamide, an appetite stimulant, and stimulates the release of α -MSH, an appetite-antagonist [26,45]. Thus, leptin promotes anorexic behavior and is intricately involved in the satiety following a meal.

Serum leptin levels are not dependent on the short-term caloric intake; leptin levels are more reflective of an individual metabolic profile over time and are dependent on the amount of existing adipose tissue. More obese individuals have very high levels of circulating leptin, and exogenous leptin treatment in these patients produces little or no weight loss [46]. Impaired leptin action in obesity is termed leptin-resistance and contributes to the difficulty of the most traditional obesity therapies to induce weight loss without symptoms of hyperphagia. Several studies have shown resolution of the leptin-resistance status after bariatric surgery procedures. Leptin levels decrease significantly especially in subjects who have had gastric bypass surgery and correlate with the percentage of weight loss. The immediate reduction in plasma leptin might result also from exclusion of nutrients contact with the fundic mucosa, leptin being produced also in the gastric fundus [47].

Obesity is also associated with a state of chronic, low-grade inflammation. Adipose tissue produces proinflammatory cytokines such as *interleukin-6* (IL-6) and tumor *necrosis factor- α* (TNF- α), mainly secreted from visceral adipose tissue. Traditionally it

has been proposed that inflammatory stimuli released by visceral fat contribute to the pathogenesis of insulin resistance in obesity.

There are trials showing that obese patients with T2DM experienced a reduction in C-reactive protein (CRP), IL-6 and soluble intercellular adhesion molecule-1 (sICAM-1) concentration after bariatric surgery [48,49].

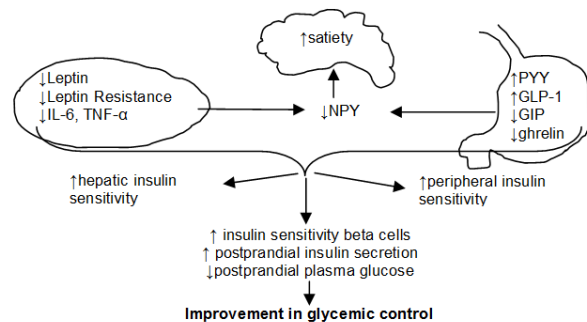


Figure 1. Summary of mechanisms responsible for improvement in glycemic control after bariatric surgery.

Conclusion

As we know, bariatric surgery is a valuable treatment option in obese patients, but it does not replace lifestyle, behavioral, and medical treatments. However, these methods should not be thought of as a last resort treatment, especially when other obesity-related co-morbidities are poorly controlled.

After many years, bariatric surgery has emerged as an impressive treatment for T2DM and provides an opportunity to explore the mechanisms involved in generating sustained improvements in glycemic control. Development of clinical pathways for the integration of bariatric procedures into the management of diabetes and obesity is needed, as are clinical studies to establish the predictors of surgical success and failure and the best regimens for diabetes management after bariatric surgery. In addition, robust

criteria for selection of the patients and prioritization for surgery should be established.

Furthermore, the durability of weight loss after surgery and its effects on progressive

loss of B-cell function, microvascular complications, the long-term effect on macrovascular complications and overall mortality should be assessed.

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