

Mechanism of diabetes control after metabolic surgery

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Abstract: Gastrointestinal metabolic surgery is becoming the most effective therapy for type 2 diabetes (T2D) in obese patients. Mechanism underlying the glycemic control of metabolic surgery is intriguing and has been heavily investigated but still not well defined. Multiple plausible mechanisms, rather than a single predominant mechanism, likely mediate the early and long-term glycemic control after metabolic surgery. This paper examines the proposed mechanism from published research findings. Bariatric surgery consisted of three parts of anatomical changes: (I) gastric restriction; (II) exclusion of duodenum and upper intestine; (III) rapid delivery of food to distal intestine or short common channel. These anatomical changes may induce a lot of physiologic and molecular changes helping in the resolution of T2D. The proposed mechanisms included calories restriction and weight loss, ghrelin, duodenum exclusion effect with gastrointestinal (GI) tract nutrient sensing, rapid distal nutrient delivery with gut hormone response, changes in bile acid metabolism, and intestinal microbiome. These changes, acting through peripheral and central pathway, result in reduced hepatic glucose, increased tissue glucose uptake, improved insulin sensitivity, and enhanced B-cell function. Different procedures may provide different mechanism and help in identifying novel therapeutic targets.

Keywords: Mechanism; type 2 diabetes (T2D); metabolic surgery

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Introduction

The notion that gastro-intestinal (GI) surgery may alter glucose tolerance curve in peptic ulcer patients was first reported in 1930's (1). Then, Evensen described the development of hypoglycemia several years after gastrectomy for peptic ulcer disease in 1942 (2). Increased insulin sensitivity as the underlying mechanism was proposed. However, the initiation of metabolic surgery started from the report by Pories *et al.* in 1995 (3). In this landmark paper, the authors reported that gastric bypass is the most effective therapy for type 2 diabetes (T2D) in morbidly obese patients and 90% of them remained diabetes free 10 years later. He suggested that caloric restriction played a key role and the relative Rubino, then, rejuvenated

the metabolic surgery by publishing the provoke concept of duodenum exclusion for the treatment of diabetes by an elaborate animal experiment in 2004 (4). Historically, bariatric operations were thought to promote weight loss by causing gastric restriction and/or mal-absorption. However, discrete parts of GI tract differentially influence glucose homeostasis and may be influenced by various types of bariatric/metabolic procedures. Rubino's study initiated many elaborated basic studies, in parallel with establishment of the GI tract as a key regulator of energy and glucose homeostasis, improved the understanding of the mechanism of T2D remission after metabolic surgery. Diabetes remission after metabolic surgery results from improvement in both insulin resistance and beta-cell dysfunction, mainly

the increase in early phase insulin release (5,6). Nevertheless, the dramatic resolution of T2D was induced by the interaction of multiple organ-related pathways involving the brain, gut, liver, pancreas, muscle, adipose tissue and others (7-9). Different type of metabolic surgery have different degree of their improvement and provide a best chance for scientist to investigate the mechanism involved in T2D remission after surgery. Understanding which part of the anatomical rearrangement of GI metabolic surgery is essential for the glycemic control of T2D and may help us to elucidate the molecular mechanism of T2D control. Despite a lot of progress in the past decade, the physiology of remission is still incompletely understood. This review will describe the anatomic and physiologic changes in GI metabolic surgery. The main proposed hypotheses of the possible mechanism underlying the glycemic effects of metabolic surgery are also discussed below.

Anatomic changes and GI reroute

Metabolic surgery is a GI surgery and its effect is through various GI anatomic changes and reroute. It can be summarized into:

Gastric restriction

Intestinal total bypass was the first bariatric surgery but failed in high incidence of severe malnutrition causing protein deficiency, liver cirrhosis and mortality (10). Instead of total intestinal bypass, partial jejunioileal bypass was proposed for the control of hyperlipidemia (11). This procedure was effective in lipid control and only a minimal weight loss effect at 25-year follow-up. Vertical banded gastroplasty (VBG) was the first successful bariatric procedure with a pure gastric restriction effect. Laparoscopic adjustable gastric banding (LAGB) is another pure gastric restrictive procedure. Both procedures can provide about an average of 15% total weight loss in a long-term but many patients required revision for weight regain (12). The gastric restrictive effect of gastric bypass was provided by a small gastric pouch and small gastro-jejunal anastomosis. Weight regain after gastric bypass was commonly attributed to dilated gastric pouch and wide anastomosis (13). Proposed management of weight regain after gastric bypass were resizing the gastric pouch or endoscopic downsizing the gastrojejunostomy (14,15). Therefore, gastric restrictive effect was considered to be

the most important part of metabolic surgery and consisted about 70% of the effect of gastric bypass (16).

Exclusion of duodenum and upper intestine

Duodenum and upper intestine plays an important role on nutrient absorption and glycemic control through a complex series of hormonal and neural responses (9). The duodenum and upper jejunum sense nutrients and initiate feed-back mechanisms through a gut-brain-liver neuron axis to regulate glycemia (17). The pathophysiology of T2D may be due to a malfunction of duodenum glycemic regulation mechanism (4). Reroute the GI tract by Roux-en-Y reconstruction cause exclusion of duodenum and upper part of the jejunum from exposure to ingestion nutrients. This anatomic change may change the physiologic response of digestive enzyme secretion from duodenum, gut hormone changes and nutrient sensing of upper small intestine (18,19). For example, duodenojejunal bypass (DJB), was a procedure to exclude the duodenum and proximal jejunum without gastric restriction, improved glycemic control without reduction of food intake and weight loss (20). A recent developed new device, duodenum jejuna sleeve tube, also had the similar effect as DJB (21).

Rapid delivery of food to distal intestine or short common channel

Reroute GI tract of gastric bypass not only exclude the duodenum but also exclude the function of pylorus. Therefore, may rapidly deliver incompletely digested food to the distal bowel which may induce a strong gut hormone change, mainly glucagon-like peptide (GLP-1) and peptide YY (PYY) (22,23). This effect may also cause the fluctuation of bile acid and change of microbiota (24,25). Interestingly, sleeve gastrectomy was found to have this effect without reroute GI tract possibly due to rapid intestine transit time (26).

Mechanism of effect

Overwhelming evidence have supported that effective diabetes resolution was achieved in obese T2D patients after undergoing metabolic surgery. The underlying mechanism for diabetes remission after metabolic surgery is intriguing. Initially, five possible mechanisms had been proposed, including the starvation-followed-by weight-

loss hypothesis, the ghrelin hypothesis, the lower intestinal (hind-gut) hypothesis and the upper intestinal (fore-gut) hypothesis. More theories were proposed recently, including bile acid and microbiota. None of these theories necessarily precludes the others. Therefore, any combination of these mechanisms may contribute to some degree in T2D remission and it is very difficult to design a study to elucidate the exact mechanism. The main proposed mechanism underlying the glycemic effects of metabolic surgery are discussed below.

Calorie restriction and weight loss

The gastric restriction part of various type of metabolic surgery may contribute to calorie restriction and subsequent weight loss which can have potent effects on insulin sensitivity. Simply calorie restriction to 1,100 kcal/d for 48 h could result in improved hepatic insulin sensitivity with reduced hepatic gluconeogenesis (27). A longer calories restriction with very low-calorie diet (VLCD) of 500 kcal/d may not only improve insulin resistance but also beta-cell function, evident by restoration of early phase insulin secretion (28). Using VLCD up to 8 weeks may reduce the pancreatic fat content which can restore the first-phase insulin secretion of T2D patients (29,30). However, improvement of skeletal muscle insulin resistance required greater weight loss (>20%) after gastric bypass or gastric banding (31,32).

Ghrelin effect

Ghrelin is an orexigenic gut hormone mainly secreted from the gastric fundus and displays a cyclic rhythm with an increase before meals and decrease after meals. Ghrelin has been shown to have diabetogenic effects because ghrelin injection in human suppresses insulin secretion and may induce hyperglycemia (33). It was found that weight loss induced by diet control may lead to compensatory homeostatic changes, including increased hunger, increased circulating ghrelin, and reduced circulating GLP-1 and PYY (34). These changes are likely to contribute to the high degree of weight recidivism with dieting. However, ghrelin is undoubtedly decreased long-term after fundus resection which may play an important role in the sustainable effect of weight after sleeve gastrectomy (35,36). The data after gastric bypass are inconsistent and contradict each other when the gastric segment is disconnected from food contact but not resected in gastric bypass procedure (37-39).

Therefore, the maintenance of weight loss after gastric bypass may rely on the change of GLP-1 and PYY than ghrelin (21,40).

Foregut effect

Duodenum and upper intestine plays an important role on glycemic by incretin effect. Incretin effect is a phenomenon known as when oral glucose will promote greater insulin release than dose isoglycemic glucose administered parentally. Incretin effect is predominantly mediated by the incretins GLP-1 and gastric inhibitory polypeptide (GIP). Anti-incretin or decretin was first proposed by Rubino to play as a counterbalance the effects of incretin (41). Patients with T2D are characterized by a blunt incretin effect control and may be due to the overproduction of anti-incretins and can be treated by duodenum exclusion (4). Many clinical studies supported the efficacy of duodenum exclusion on T2D treatment (20, 42-44). Although specific human anti-incretins have not yet been found, a strong candidates, name as decretin, was recently been identified in animal (45). DJB tube was a concept pioneered by Rubino for the treatment of T2D in animal model (46). A recent developed new device, duodenum jejuna sleeve tube or liner, was demonstrated having a similar glycemic control effect in human (21). Duodenum exclusion might create a biliopancreatic (BP) limb which consisted of duodenum and upper intestine without food exposure. The role BP limb is intriguing because the finding of nutrient sensing and gut-brain talk of upper jejunum (17). A recent animal study reported the importance of BP limb length, the longer the better, in glycemic control (47). A more important finding of this study was the existing of BP limb is essential for the glycemic control because excision of the BP limb will abolish the glycemic effect.

Hindgut effect

The rapid delivery of nutrients to the distal bowel will stimulate the secretion of GLP-1 and PYY. GLP-1 is an incretin hormone, promoting post-prandial insulin release and improving pancreatic beta cell function. GLP-1 is suppressed in T2D (48) and GLP-1 agonists is now widely used in the treatment of T2D (49). Some reports using elegant study design have found that GLP-1 is playing a significant role in T2D resolution after gastric bypass (50,51). This response was also observed after sleeve gastrectomy (22,23). However, the role of GLP-1 in T2D resolution after metabolic surgery

was questioned by some reviews (52,53) as well as in some studies of mouse in which GLP-1 was not required for either T2D resolution or weight loss after bypass or sleeve gastrectomy (54-56).

PYY is an anorexic hormone co-secreted with GLP-1 from the "L-cell" of distal bowel in response to nutrients. PYY acts to decrease food intake with faster satiation and may reduce insulin resistance. The elevation of PYY was usually associated with the elevation of GLP-1 but was not observed after gastric banding (57).

Recent studies had shown that hindgut theory might involve the molecular mediator that ameliorated T2D, including bile acid and microbiota. These two important molecular mechanisms will be discussed in following.

Bile acid

Bile acids are synthesized from cholesterol in the liver and secreted into duodenum through bile duct to facilitate the absorption of lipids via formation of micelles. Most of the bile acid (95%) was absorbed from small bowel and recycling of bile acid occurs about 6–12 times per day. Bile acids not only function in lipid absorption but also play an important role in glucose metabolism. Bile acids are a ligand of the farnesoid X receptor (FXR) in the liver and small intestine, affecting hepatic metabolism and G-protein-coupled bile acid activated receptors (TGR-5) of the L-cell and promoting the release of incretin (58-60). Systematic bile acid levels were found to be elevated in patients following gastric bypass but not in gastric banding (56,61-63), suggesting an increase stimulation of FXR after gastric bypass. In contrast to systematic reaction, bile acid release in the gut can selectively activates intestinal FXR and promotes adipose tissue browning, reduces obesity and insulin assistance (64). Bile acid was found in many clinical studies and animal models support the key role of bile acids and bile acid receptor is a potential target for new drug development (65). Recently FXR has also been shown to be the key role for the anti-diabetic effect of sleeve gastrectomy (66). Bile acids signaling through FXR may be a common mechanism involved in the mechanism of bariatric/metabolic surgery. Further delineation of the molecular mechanisms underlying these beneficial effects could provide targets for the development of new nonsurgical treatments.

Microbiota

Bacteria colonize the gut soon after birth and become

stabilized after the age 2. The gut microbiota was recently recognized to play an important role in energy metabolism and might contribute to the epidemics of obesity and T2D (67). Studies have demonstrated that obesity is associated with increased Firmicutes and decreased Bacteroides levels compared with normal person (68,69). In addition, obesity was also found to have reduced bacterial diversity (70). Bariatric surgery was found to decrease firmicutes and increase Bacteroides level, as well as increase the bacterial diversity (71,72). However, these changes can also be induced by diet changes (73,74). Another factor which may contribute to the change of microbiota after surgery is the change of bile acid concentration and fecal composition in distal gut. Fecal waters were found to be highly cytotoxic after surgery which may cause change of microbiota (75). A study in human observed that change of bile acid concentration and composition was associated with dysbiosis of the gut microbiota (76). Overall, it seems that surgery induced food intake change, weight loss and GI reroute all have important role in microbiota composition after metabolic surgery but microbiota change is more like to a result rather than a cause.

Conclusions

The success of metabolic surgery for the treatment of T2D depends on several mechanisms. Three important anatomic changes after metabolic surgery may initiate several important mechanisms for T2D remission. Gastric restriction is the first important anatomic change which will induce decreasing calories intake and followed by weight loss. Decrease of ghrelin after sleeve gastrectomy may be important in prevention of weight regain. Duodenum and upper intestine exclusion is the second anatomic change which may decrease fat absorption, change bile acid entero-hepatic flow. Rapid delivery food to distal bowel is the third anatomic change which will induce the GLP-1 and PYY changes but more important may be the change of bile acid recycle and increase bile acid blood level. Bile acid is a molecule that may play an important role in T2D remission after metabolic surgery. Further studies through the application of detailed phenotyping, genomics, metabolomics, and gut microbiome studies will enhance our understanding of metabolic surgery and help identify novel therapeutic targets.

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