



Current Perspective

A perspective on metabolic surgery from a gastroenterologist

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ABSTRACT

Type 2 diabetes (T2D) and obesity are important public health problems. The global prevalence of diabetes mellitus is 8.8%. Interventional diabetology and obesitology have been recently advocated as treatment options for T2D and obesity. The roles of metabolic surgery such as Roux-en-Y gastric bypass, sleeve gastrectomy, gastric banding, and biliopancreatic diversion are focused. Different types of metabolic surgeries have different glucose-lowering and weight loss effects. Endoscopic treatments include the intra-gastric balloon (to restrict the gastric volume) and duodenal-jejunal bypass liner (DJBL, as a malabsorptive procedure). Anatomic changes in the gastrointestinal tract may cause alterations in gut hormones, bile acids, adipokines, inflammatory cytokines, hepatokines, myokines, gut microbiota, and even unidentified factors. Modulating gut hormones, including foregut (ghrelin, glucose-dependent insulinotropic polypeptide) and hindgut (glucagon-like peptide-1, peptide YY) hormones, through metabolic surgeries improves glycemic homeostasis. Metabolic surgeries reduce pro-inflammatory cytokines and increase anti-inflammatory cytokines. Metabolic surgeries also regulate one's appetite through the new establishment of jejunal nutrient sensing. Therefore, the effects of metabolic surgery and DJBL implantation emphasize the crucial role of the small intestine in glucose homeostasis. Removing diabetogenic or obesogenic factors from the duodenum and/or jejunum may help to solve the problems of diabetes and obesity in the future.

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1. Introduction

Type 2 diabetes (T2D) and obesity are the most important public health problems facing the world today, and they are the primary causes of mortality, morbidity, disability, and discrimination in human health care, education, and employment. According to the International Diabetes Federation, the global prevalence of diabetes mellitus was 8.8% in 2015, affecting more than 415 million people worldwide and almost 153 million people in the Western Pacific region (1). However, the effects of

traditional treatment for T2D and obesity, including lifestyle modification and medications, are limited. Among treatment for T2D, lifestyle modification still plays a key role, although it is not more effective and sustainable than medications. Only about 14.6% of lifestyle intervention participants had partial or complete remission within the first year, and 3.4% had partial or complete remission after 4 years according to Gregg et al.'s study (2). Therefore, interventional diabetology and obesitology have been recently advocated as treatment options for T2D and obesity (3). Between these treatment options, metabolic surgery is the only effective and long-lasting way to remit T2D and lose excessive body weight (4). More evidence has shown that alteration of the gastrointestinal tract anatomy changes the intrinsic regulatory mechanism of glucose homeostasis (5). Therefore, we have written the current perspectives article from the viewpoint of a gastroenterologist to address the emerging importance of interventional diabetology in remitting human T2D.

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2. Roles of metabolic surgery

Metabolic surgery and other interventional diabetology includes several types such as Roux-en-Y gastric bypass (RYGB, Fig. 1A), sleeve gastrectomy (SG, Fig. 1B), gastric banding (Fig. 1C), biliopancreatic diversion (BPD, Fig. 1D), intra-gastric balloon (IGB, Fig. 1E), and duodenal-jejunal bypass liner (DJBL, Fig. 1F). The types of surgery are divided into malabsorptive procedures, restrictive volume procedures, and mixed procedures. Different types of metabolic surgeries have different glucose-lowering effects, according to several studies (6–8). A meta-analysis showed different efficacies of T2D remission in patients who underwent BPD (95.1%), RYGB (80.3%), and gastric banding (56.7%) (9). In our previous randomized, controlled trial, we also found greater T2D remission in patients who underwent single anastomosis gastric bypass (GB) than those who underwent SG at 12 months (93%), 2 years (81%), and 5 years postoperatively (60%) (3–5). More collective data

suggest that malabsorptive type bariatric procedures that bypass the foregut, especially the duodenum (e.g., GB), seem to play a better role in diabetes remission and weight loss than only procedures that restrict gastric volume. However, surgery that restricts gastric volume still plays a role in T2D. In a 17-year retrospective study, surgery that restricted gastric volume such as gastric banding was associated with reduced mortality in diabetic and non-diabetic patients, as well as a decreased incidence of diabetes and cardiovascular diseases (10). Metabolic surgery permanently resets strong counter-regulatory responses such as hunger and cravings by re-sensitizing homeostatic regulatory circuits in the hypothalamus and hedonic-motivational processing in cortico-limbic systems through changes in gut-brain signaling, leading to differential nutrient handling and energy partition postoperatively (11).

In addition, treatment methods that use endoscopy to restrict the gastric volume such as IGB or as malabsorptive procedures such as DJBL emerge. The IGB procedure was first used in 1985 for

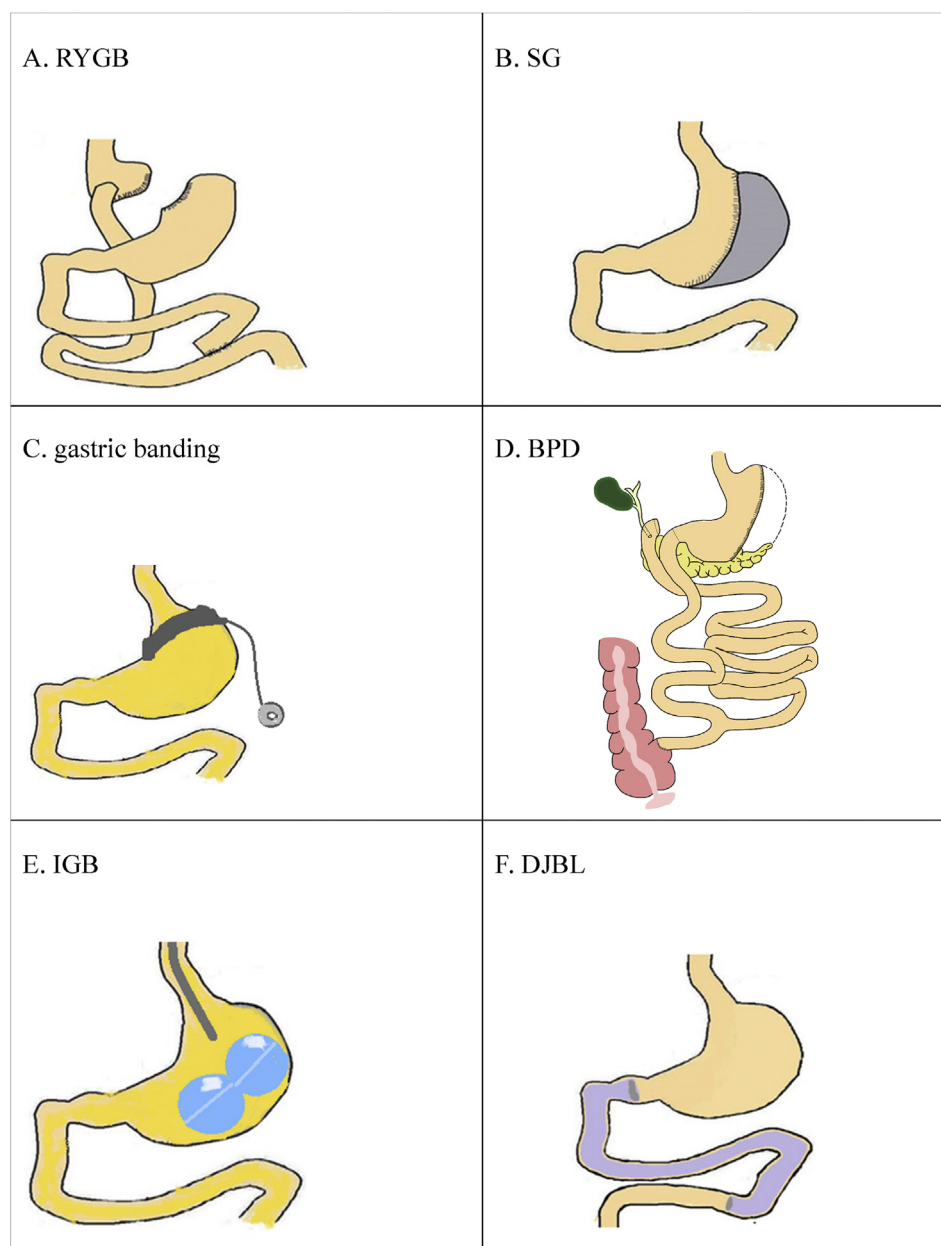


Fig. 1. Diagrams illustrating different surgical and interventional medical treatment for type 2 diabetes in humans: (A) Roux-en-Y gastric bypass (RYGB), (B) sleeve gastrectomy (SG), (C) gastric banding, (D) biliopancreatic diversion (BPD), (E) intra-gastric balloon (IGB), and (F) duodenal-jejunal bypass liner (DJBL).

obesity (12). In 2015, the Food and Drug Administration (FDA) approved non-surgical temporary balloon devices (e.g., the ReShape Dual Balloon and Orbera Gastric Balloon) to treat obesity. It may serve as an adjunct for managing overweight patients with poorly controlled T2D, but weight regain is commonly observed during the long-term follow-up after IGB removal (13). Conversely, the DJBL procedure is a newer treatment method, and it was first used in 2009 for obesity (14). However, it has not been approved yet by the FDA. According to de Jonge et al.'s study, markedly decreased fasting glucose and postprandial glucose levels were observed in patients with T2D undergoing DJBL (15). Some complications such as liver abscess were reported after the DJBL procedure (16). Any anatomic changes in the gastrointestinal tract can cause alterations in gut hormones, bile acids, adipokines, inflammatory cytokines, hepatokines, myokines, gut microbiota, and even unidentified factors (17).

3. Functions of gut hormones

Through the embryological origin of each part, the gastrointestinal tract is divided into foregut, midgut, and hindgut. Modulating gut hormones through metabolic surgeries, including foregut hormones (ghrelin, nesfatin-1, cholecystokinin, and glucose-dependent insulinotropic peptide) and hindgut hormones (glucagon-like peptide-1 [GLP-1] and peptide YY [PYY]) may increase satiation, promote digestion, and improve glycemic homeostasis (18,19). In our previous articles, we found that ghrelin levels increased after RYGB due to weight loss, but they decreased after SG due to gastric resection (8,18). In most studies, the GLP-1 and PYY concentrations increased, demonstrating a hindgut effect (18,19). However, different gut hormone results were found when the IGB procedure was performed through endoscopy. Konopko-Zubrzycka et al. demonstrated that weight loss induced by IGB was associated with a decrease in the plasma leptin level and a transient increase in the plasma ghrelin level in patients with morbid obesity (20).

4. Immunometabolism and unidentified factors

Emerging evidence has shown that GB and SG can reduce pro-inflammatory biomarkers and increase the anti-inflammatory mediators of obesity. Concentrations of leptin, C-reactive protein, and tumor necrosis factor- α decreased, while the adiponectin levels increased 6 months after GB (19,21). Incretins play important roles in glucose homeostasis by stimulating a decrease in blood glucose levels. The effect of incretins causes pancreatic β -cells to release insulin and pancreatic α -cells to inhibit glucagon release after eating. However, another study showed that nutrient passage through the gastrointestinal tract can activate negative feedback mechanisms (anti-incretins) to counterbalance the effects of incretins and prevent postprandial hyperinsulinemic hypoglycemia (22). They also found unidentified protein extracts (anti-incretins) from the duodenum and/or jejunum of diabetic rodents and humans that induce insulin resistance in cell-based assays and in vivo (22). This observation supports the hypothesis that the proximal small bowel of patients with T2D may produce diabetogenic factors, which is consistent with the anti-incretin theory.

5. Appetite regulation

Patients undergoing metabolic surgery have an anorectic status that facilitates weight loss and improves glucose homeostasis. The area under the curve (AUC) for patients' hunger sensation (AUC_{0–180}) decreased, and the fullness sensation of AUC_{0–180} increased after RYGB surgery (23). The Visual Analogue Scale scores

of patients' appetites decreased after RYGB and SG surgery (24). According to le Roux et al.'s study, a pleiotropic endocrine response may contribute to improved glycemic control, appetite reduction, and long-term changes in body weight (25). In addition, it has been hypothesized that jejunal nutrient sensing can be newly established after metabolic surgery by correcting duodenal nutrient sensing defects in patients with obesity and T2D (26). Our randomized, controlled trial also demonstrated that patients with T2D after either GB or SG exhibit distinct nutrient-induced consumption behaviors and appetite sensations post-operatively, in which ABCD score plays some role (27).

6. Conclusions

The International Diabetes Federation estimates that the number of patients with diabetes will increase to more than 642 million worldwide by 2040 (1). Effective treatment methods for controlling diabetes are greatly needed. Concurrent glucagon or GLP-1 receptor agonists, advanced GLP-1 agonists, and targeting intestinal L-cell secretion and differentiation (through gut microbiota) are popular topics of ongoing research. Decreased weight and adiposity is transmissible through the gut microbiota independent of food intake in rodents, whereas gut microbiota richness increases after RYGB in obese humans; thus, intestinal bacterial and fungal microbiota transplantation may be promising to treat diabetes and obesity. Recently, bile acids have emerged as an important regulator for explaining improved glucose homeostasis and weight loss after metabolic surgery. The exploration of bile acids, especially their subtype analysis, is a new direction of research. If manipulated properly, gut hormones, gut bacterial and fungal microbiota, and bile acids can exert unparalleled control on the human appetite, metabolism, and well-being.

Therefore, effects of metabolic surgery and DJBL implantation emphasize the crucial role of the small intestine in glucose homeostasis (18,28–31). As the crucial role of the small intestine in remitting diabetes cannot be neglected, removing diabetogenic or obesogenic factors such as protein secreted from the duodenum and/or jejunum, as well as duodenal exclusion through endoscopic DJBL using tissue-compatible, self-degraded material may help solve the problems of diabetes and obesity in the future.

Conflicts of interest

The authors indicated no potential conflicts of interests.

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