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A Gut Feeling to Cure Diabetes: Potential Mechanisms of Diabetes Remission after Bariatric Surgery

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A cure for type 2 diabetes was once a mere dream but has now become a tangible and achievable goal with the unforeseen success of bariatric surgery in the treatment of both obesity and type 2 diabetes. Popular bariatric procedures such as Roux-en-Y gastric bypass and sleeve gastrectomy exhibit high rates of diabetes remission or marked improvement in glycemic control. However, the mechanism of diabetes remission following these procedures is still elusive and appears to be very complex and encompasses multiple anatomical and physiological changes. In this article, calorie restriction, improved β-cell function, improved insulin sensitivity, and alterations in gut physiology, bile acid metabolism, and gut microbiota are reviewed as potential mechanisms of diabetes remission after Roux-en-Y gastric bypass and sleeve gastrectomy.

Keywords: Bariatric surgery; Diabetes mellitus, type 2; Obesity; Roux-en-Y gastric bypass; Sleeve gastrectomy

INTRODUCTION

A potential cure for diabetes has arisen in an unexpected way. As diabetologists, we have tried to determine the pathophysiology of type 2 diabetes so that we can normalize glucose homeostasis without using any oral or injected medications. However, the results of our ceaseless efforts leave us far from a cure. With heart-aching disappointment in mind, we have practiced within a paradigm of "care not cure," which suggests that a cure is impossible to attain but that care is currently the best option. In 1995, Dr. Pories published a paper with a somewhat provocative title, "Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus [1]." At that time, Dr. Pories observed a drastic improvement in blood glucose levels after Roux-en-Y gastric bypass (RYGB) in obese subjects who had diabetes or impaired glucose tolerance. This was the earliest glimpse of a potential diabetes cure by surgical treatment. In a meta-analysis performed in 2004 including approximately 5,000 patients with type 2 diabetes [2], diabetes remission was observed in 76.8% of obese patients with type 2 diabetes who underwent any type of bariatric surgery. However, diabetes remission rates differed according to the type of surgery that patients received (47.9% for gastric banding, 71.6% for vertical banded gastroplasty, 83.7% for RYGB, and 98.9% for biliopancreatic diversion [BPD]) [2], which implies that the mechanism of diabetes remission is complex and encompasses a variety of anatomical, physiological, and molecular changes. In a recent randomized controlled trial with obese type 2 diabetes patients [3], the rate of diabetes remission (defined as a fasting glucose level of <100 mg/dL and an hemoglobin A1c (HbA1c) level of <6.5% with no antidiabetes medications) was 0% with medical therapy alone, 75% with RYGB, and 95% with BPD. In a 1-year randomized controlled trial in obese patients with uncontrolled type 2 diabetes [4], both RYGB and sleeve gastrectomy (SG) achieved improved glycemic control, defined as an HbA1c level of <6.0%, more frequently (42% and 37% of patients, respectively) than medical therapy alone (12% of patients). Therefore, bariatric surgery has evolved into metabolic/diabetes surgery. Furthermore, the benefits of bariatric surgery extend far beyond glycemic control. In the Swedish

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Obese Subjects Study, mostly composed of patients who underwent vertical banded gastroplasty, risk factors for cardiovascular diseases, including high blood pressure, dyslipidemia, hypercholesterolemia, and hyperuricemia, were greatly reduced at 2 years postsurgery, and these effects persisted over 10 years after surgery [5]. Furthermore, bariatric surgery reduced all-cause mortality [6], cardiovascular events and mortality [7], and the incidence of cancer [8]. Bariatric surgery was also effective in preventing type 2 diabetes [9] and in reducing microvascular and macrovascular complications [10]. Overall, bariatric surgery improved the quality of life in obese subjects [11]. In the following article, I would like to present a succinct review regarding the current understanding of the mechanism of diabetes remission after bariatric surgery focused on RYGB and SG.

CHARACTERISTICS OF RYGB AND SLEEVE GASTRECTOMY

RYGB isolates approximately 95% of the stomach from the passage of food; therefore, a gastric pouch with approximately 5% of the total stomach volume receives orally ingested food. The configuration of RYGB shown in Fig. 1A consists of the Roux limb or alimentary limb, the biliopancreatic limb, and the common channel. In the common channel, the orally ingested food meets digestive enzymes secreted by the pancreas and bile acids secreted by the hepatobiliary system. Thus, the RYGB procedure (1) restricts the amount of food intake; (2) bypasses most of the stomach, duodenum, and proximal jejunum; and (3) expedites the passage of unabsorbed nutrients to the distal intestine where glucagon-like peptide-1 (GLP-1) and peptide-YY (PYY) secreting L-cells are abundant. Indeed, GLP-1 and PYY secretion is markedly increased after RYGB.

The SG procedure removes approximately 75% of the stomach to restrict food intake (Fig. 1B). With this surgery, the intragastric pressure increases upon ingestion of foods, which in turn increases the tension of the gastric wall [12]. Both gastric emptying and intestinal transit are markedly increased after SG [12]. Interestingly, GLP-1 secretion is noticeably augmented with SG, even though the anatomy of the gastrointestinal tract is not altered except with regard to the restriction of gastric volume. Rapid gastric emptying may contribute to the increased GLP-1 secretion. However, direct intraduodenal infusion of dextrose increased GLP-1 secretion in mice subjected to SG relative to control animals, which indicates that altered gastrointestinal physiology independent of altered gastric emptying plays an important role in the exaggerated GLP-1 response after SG [12].

POTENTIAL MECHANISMS OF DIABETES REMISSION FOLLOWING BARIATRIC SURGERY

Decreased calorie intake and weight loss

RYGB typically results in 35% to 40% body weight loss from baseline and 50% to 80% excess body weight loss [13]. Howev-

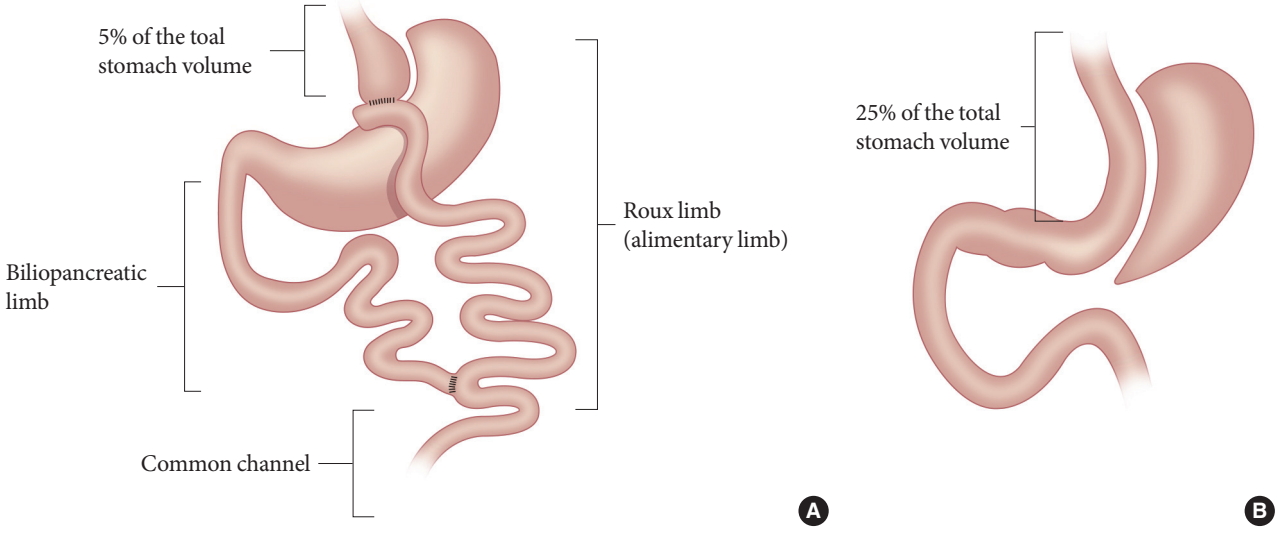

Fig. 1. Schematic representation of (A) Roux-en-Y gastric bypass and (B) sleeve gastrectomy.

er, a dramatic improvement in glucose control frequently occurs immediately after the surgery, usually within 1 week, when significant weight loss has not yet taken place [1,14]. Therefore, the mechanism of immediate diabetes remission or improvement appears to be weight loss-independent. However, adjustable gastric banding (AGB) is typically accompanied by a gradual improvement in glucose control in obese type 2 diabetes patients [15], which is in contrast to results observed from RYGB. The discrepancy in the time-course of diabetes remission between RYGB and AGB suggests that there are mechanisms other than weight loss *per se* for the rapid remission or improvement of diabetes after RYGB. However, it was shown that calorie restriction is required for rapid improvement in insulin sensitivity immediately after RYGB (within 1 week) by comparing the effects of calorie restriction and RYGB in obese subjects [16]. Similarly, in a within-subject time series study comparing the effects of calorie restriction and RYGB, both treatments resulted in similar marked improvements in glucose homeostasis in obese type 2 diabetes patients [17]. In addition, when nondiabetic obese subjects achieved 20% weight loss from baseline after either RYGB (average 16±2 weeks after surgery) or AGB (average 22±7 weeks after surgery), similar changes in β-cell function, insulin sensitivity, and gene expression in adipose tissue were observed [18], which indicates that weight loss is important in improved glucose homeostasis. However, both calorie restriction without surgical stress [16,17] and weight loss in nondiabetic subjects [18] have substantial limitations in recapitulating the processes that occur in obese type 2 diabetes patients after RYGB. Nevertheless, acute energy restriction and long-term weight loss play an important role in the improvement of glucose homeostasis following RYGB [19].

Changes in gut physiology

As explained earlier, RYGB causes enormous changes in the gastrointestinal anatomy, and therefore, altered gastrointestinal physiology is expected to occur after surgery. In this regard, both foregut and hindgut factors have been suggested as important players [13]. Although many factors have been demonstrated to independently contribute to the remission of diabetes from a reductionist's point of view, careful interpretation from a holistic point of view is necessary because many anatomic, physiologic, and molecular changes coalesce after bariatric surgery.

Ghrelin is the only orexigenic gastrointestinal peptide secreted mainly from the gastric fundus. Evaluation of ghrelin secretion in patients after RYGB showed mixed results, perhaps due to different surgical techniques [13,20]. Therefore, intuitively, the role of ghrelin appears to be dispensable during diabetes remission after RYGB. However, in patients who receive SG, which removes most of the ghrelin-producing tissue, a marked and persistent decrease in ghrelin secretion is typically observed [21]. Yet, SG influences appetite, body weight, and glucose metabolism even in ghrelin knockout mice [22]. Therefore, ghrelin is unlikely to be a critical factor in diabetes remission after bariatric surgery.

As illustrated in Fig. 1A, one of the components of RYGB is the exclusion of the duodenum and the proximal jejunum from the passage of food. To examine the role of excluding the duodenum and upper jejunum, an experimental procedure called the duodenal-jejunal bypass (DJB) surgery was created and tested in Goto-Kakizaki rats, a nonobese type 2 diabetic animal model. With this elegant surgical model, the exclusion of the duodenum and proximal jejunum without gastric volume restriction exhibited significant improvement in glycemic control in Goto-Kakizaki rats [23,24]. Although DJB was designed to assess the contribution of the upper small intestine to improvements in glucose homeostasis after RYGB [23,24], exendin$_{9\text{-}39}$, a GLP-1 receptor antagonist, abolished the glucose-reducing effect of DJB [25]. This finding suggests that GLP-1, a representative hindgut hormone, is critical in mediating the glucose reduction resulting from DJB. Interestingly, it was reported that the number of K/L cells, which produce both GIP and GLP-1, was increased in the jejunum attached to the stomach in Goto-Kakizaki rats after DJB [26], indicating that GLP-1 secreted from this proximal intestinal segment may improve glucose homeostasis. Although GLP-1, a typical hindgut hormone, is important in improved glucose homeostasis after DJB, proteins obtained from the duodenum of *db/db* mice or insulin-resistant humans trigger insulin resistance both *in vitro* and *in vivo* [27]. Therefore, the so-called foregut factor (also known as anti-incretin) may contribute to the pathophysiology of type 2 diabetes. Interestingly, DJB or intrajejunal nutrient administration suppresses endogenous glucose production through the gut-brain-liver axis, presumably by stimulating the jejunal nutrient sensor [28]. Therefore, the mechanism of action of DJB is very complex. Aside from the debate whether the foregut factor or the hindgut factor is the major player in the improved glucose homeostasis after DJB, an endoluminal liner bypassing the duodenum and proximal jejunum showed promising results in body weight control and glucose metabolism in obese patients with type 2 diabetes [29].

RYGB accelerates gastrointestinal transit of ingested food and thereby stimulates L-cell secretion of GLP-1, PYY, and oxyntomodulin, which regulates energy and glucose metabolism [30]. In patients with type 2 diabetes, RYGB increased plasma levels of GLP-1, PYY, and oxyntomodulin after oral glucose load, whereas calorie restriction alone did not [31]. Just as in RYGB, plasma GLP-1 levels markedly increased after BPD [32], which also expedites the transit of orally ingested foods to the distal intestine. However, the AGB procedure, which simply restricts food intake without accelerating gastrointestinal transit, does not increase plasma GLP-1 levels [33]. Unexpectedly, SG, which had previously been considered as a mere restrictive bariatric procedure, induces a marked increase in plasma GLP-1 levels [34,35]. Accelerated gastrointestinal transit and altered gastrointestinal physiology may explain the drastic increase in plasma GLP-1 levels after SG [12]. Considering the mechanism of action of GLP-1 [36], GLP-1 could be a critical factor in weight loss and diabetes remission after RYGB. However, the administration of a GLP-1 receptor antagonist (exendin$_{9-39}$) did not reveal a significant increase in blood glucose levels in patients who showed remission of type 2 diabetes after RYGB [37], which indicates that factors other than GLP-1 may play an important role in diabetes remission following RYGB. To examine the role of the hindgut in an isolated fashion, an experimental surgical procedure called ileal transposition (or interposition) was developed [38-40]. Ileal transposition increases plasma levels of GLP-1 and PYY by promoting early contact between ingested nutrients and the ileal tissue transposed to the proximal jejunum [39-43]. However, the overall effect of ileal transposition on glucose metabolism and body weight is typically modest [38-43]. Therefore, the hindgut effect after RYGB may partly explain its diabetes remission mechanism.

Altered glucose metabolism of the intestine may partially explain the diabetes remission observed after RYGB. Increased aerobic glycolysis in the Roux limb was observed in rats treated with RYGB [44], which allows this segment of the intestine to play a major role in glucose utilization. Consistent with this finding, one of the antidiabetic mechanisms of metformin is to induce a marked increase in intestinal glucose utilization [45]. Just like the liver and the kidneys, the intestine is able to produce glucose via gluconeogenesis. Interestingly, increased intestinal gluconeogenesis, particularly in the ileum, was seen after enterogastro-anastomosis (EGA), which does not create the Roux limb, in C57Bl/6 mice fed a high-fat diet. Increased gluconeogenesis in this model was accompanied by reduced food intake, increased insulin sensitivity, and decreased endogenous glucose production [46]. It was hypothesized that the increased glucose concentration in the portal vein may explain the beneficial effects of EGA. In this process, GLUT2 appears to be essential because GLUT2 knockout mice were not subject to the metabolic effects of EGA [46]. In addition, portal vein denervation also abolished the metabolic effects of EGA [46]. Therefore, altered glucose metabolism in the intestine, either through increased glucose utilization or increased gluconeogenesis, may contribute to improved systemic glucose metabolism after bariatric surgery.

Pancreatic β-cell function

Pancreatic β-cell function is improved in obese patients with type 2 diabetes in accordance with exaggerated GLP-1 secretion immediately after RYGB and SG [47]. However, the extent of recovery of β-cell glucose sensitivity (as measured by insulin secretion rates in response to increasing plasma glucose levels) usually falls short of the normal value [48], and baseline β-cell glucose sensitivity was reported to be a major determinant of diabetes remission after RYGB [47,49]. Antagonism of GLP-1 signaling by exendin$_{9-39}$ decreases postprandial insulin secretion in these patients [50], which indicates that the restored β-cell function is largely mediated by the exaggerated GLP-1 response. Unlike the insulin response to oral glucose, the insulin response to intravenous glucose was unchanged relative to the preoperative value [51], which also highlights the importance of gastrointestinal factors in improving β-cell function. However, the disposition index (a measure of insulin secretory capacity considering the insulin sensitivity of an individual) during the frequently sampled intravenous glucose tolerance test increased mainly due to increased insulin sensitivity [52]. Although improved β-cell function after RYGB is largely ascribed to increased GLP-1 secretion, administration of exendin$_{9-39}$ hardly deteriorated postprandial hyperglycemia in patients who showed improved postprandial glycemia after RYGB [37]. Therefore, factors other than GLP-1 play a major role in improved glucose homeostasis after RYGB.

Hepatic and peripheral insulin sensitivity

Changes in insulin sensitivity after RYGB vary among different tissues. Marked improvement in hepatic insulin sensitivity was observed as early as 1 week after RYGB and persisted for up to 1 year, while the insulin sensitivity of peripheral tissues, including skeletal muscle and adipose tissue, was not changed

during the early postoperative period but improved gradually thereafter [51]. Improved hepatic insulin sensitivity is crucial in normal glucose homeostasis because it leads to decreased hepatic glucose production. Of note, hepatic insulin sensitivity dramatically improves even before any significant weight reduction occurs [51]. In this process, calorie restriction from the early postoperative period may play a critical role [53]. Although the exact mechanism of improved hepatic insulin sensitivity after RYGB is still elusive, decreased intrahepatic fat content may be responsible [54]. In a study using the euglycemic-hyperinsulinemic clamp, an improvement in peripheral insulin sensitivity after RYGB was observed only after a substantial weight loss [55]. In this regard, there appear to be many potential mechanisms for improved insulin sensitivity after RYGB [56]. Among these, weight loss-associated mechanisms are essential because improved insulin sensitivity is closely correlated with the degree of weight loss [47,51]. To summarize, hepatic insulin sensitivity improves immediately after RYGB and is largely explained by calorie restriction, while peripheral insulin sensitivity gradually improves in accordance with weight loss.

Altered bile acid metabolism

Plasma levels of bile acids are increased after RYGB [57] or SG [58], which prompted researchers to hypothesize that bile acids play a role in meditating the effects of bariatric surgery. Bile acids are known as detergents for fat absorption and routes of cholesterol elimination; however, many genomic and nongenomic actions largely related to metabolism have also been reported for this class of molecules [59]. In this regard, the nuclear receptor FXR and a G-protein coupled receptor TGR5 are known to mediate the genomic and non-genomic effects of bile acids, respectively [60]. In the absence of FXR signaling in mice, the beneficial effects of SG on body weight and glucose metabolism were abolished [61]. Further studies are needed to elucidate the exact mechanism of bile acids in weight control and glucose metabolism.

Changes in gut microbiota

The role of gut microbiota is currently discussed in terms of host-microbial interactions modulating host metabolism [62]. After bariatric surgery, a substantial change in gut microbiota has been reported not only in rodents but also in humans. In one study including humans, rats, and mice, RYGB induced rapid increases in the proportion of Gammaproteobacteria (*Escherichia*) and Verrucomicrobia (*Akkermansia*) in the gut [63]. Interestingly, a recent study showed that metformin, a representative antidiabetes medication, increased the relative abundance of *Akkermansia muciniphila* in mice [64]. However, whether metformin and RYGB similarly affect gut microbiota and thus improve glucose homeostasis is uncertain. When gut microbiota from mice subjected to RYGB were transferred to nonoperated germ-free mice, weight loss and decreased fat mass were observed [63]. However, transfer of gut microbiota from sham-operated mice to germ-free mice did not induce substantial weight loss [63]. The mechanism of weight loss via altered host-microbial interactions after RYGB is still elusive, but changes in the production of short-chain fatty acids by gut microbiota may play a role [63]. Although the causal relationship between altered gut microbiota and improved glucose control after RYGB is uncertain in humans, it is very interesting that fecal transplant from lean donors to metabolically unhealthy people improved insulin sensitivity and increased populations of butyrate-producing gut microbiota [65]. Further studies are mandatory to exploit the mechanisms of altered host-microbial interactions for the treatment of diabetes and obesity in humans.

CONCLUSIONS

The current obesity and type 2 diabetes epidemics may only be halted by breakthrough knowledge, as conventional treatments have thus far proven unsuccessful. The dramatic improvement in glucose metabolism observed following RYGB and SG prompted "gut feelings" regarding a cure for diabetes. However, such surgical procedures are not always simple and safe but sometimes cause considerable morbidity and mortality, although the incidence of complications is low. For some patients and doctors, medical treatment is preferred to surgical treatment. By elucidating the mechanisms of diabetes remission after RYGB and SG, we may be able to develop both efficacious and safe medical treatments for diabetes and/or obesity. However, our understanding of the mechanisms of diabetes remission following bariatric surgery is still very limited, although the body of knowledge is rapidly expanding (Fig. 2). It is pertinent to recall the history of antituberculosis treatment [66]. Once, thoracoplasty, which removes the ribs and collapses the diseased lung, was widely used to treat pulmonary tuberculosis but was abandoned after development of effective antimycobacterial pharmacotherapy. It is our hope that

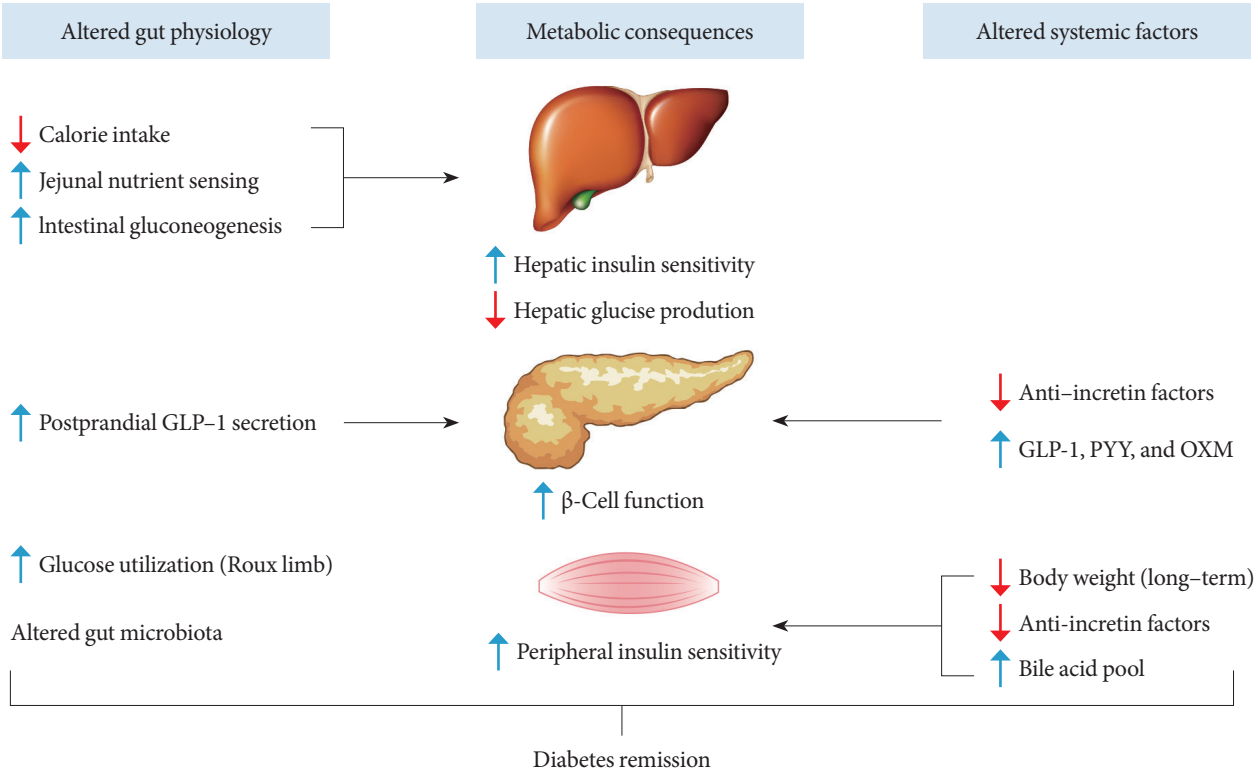

Fig. 2. Potential mechanisms of diabetes remission after Roux-en-Y gastric bypass. Altered gut physiology and systemic (or circulating) factors contribute to improved metabolic states in concert after Roux-en-Y gastric bypass. See text for detailed explanation. GLP-1, glucagon-like peptide-1; PYY, peptide-YY; OXM, oxyntomodulin.

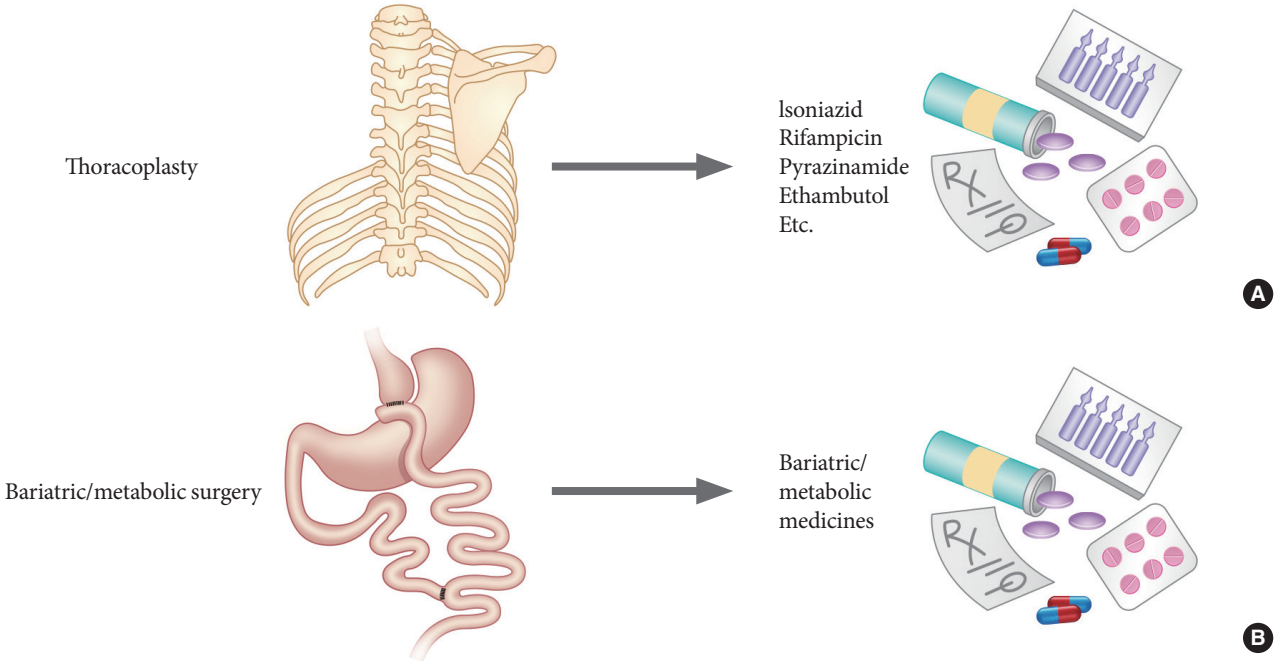

Fig. 3. Paradigm shift from surgery to medical therapy. (A) An historic example of the evolution of the anti-tuberculosis treatment and (B) the outlook for potential bariatric/metabolic medicines instead of bariatric/metabolic surgery.

bariatric surgery may be replaced by medical therapy, just as in the case of thoracoplasty (Fig. 3).

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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