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REVIEW ARTICLE

Targeting Islets: Metabolic Surgery Is More than a Bariatric Surgery

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Abstract

Metabolic surgery is an effective therapy for diabetic patients with obesity. The main mechanisms underlying the effects of metabolic surgery include food intake restriction and the accompanying reduced daily caloric intake and changes in gut hormones and bile acid. Insulin resistance and impaired β-cell function contribute to the development of type 2 diabetes. An increasing number of studies have focused on the central role of islet function in type 2 diabetes. In this article, we review the related high-quality literature and summarize the following mechanisms and principles underlying metabolic surgery in the context of islet function protection: (1) reduced glucotoxicity and chronic inflammation help facilitate better β-cell function and the preservation of β-cell mass following metabolic surgery; (2) based on the increased levels of GLP-1 and PYY after metabolic surgery, gut hormones appear to play a significant role in improving β-cell function through the GLP-1R signaling pathways; (3) the bile acid signaling pathway could affect β-cell function; and (4) the GLP-1R and bile acid signaling pathways could also cause other endocrine cells to contribute to islet function.

Keywords Metabolic surgery · Islet function · Obesity · Type 2 diabetes mellitus · Mechanisms

Abbreviations

IDF	International Diabetes Federation
T2D	Type 2 diabetes
RYGB	Roux-en-Y gastric bypass
SG	Sleeve gastrostomy
BA	Bile acid
GPCRs	G protein-coupled receptors
PKC	Protein kinase C
PKA	Protein kinase A
IRS-2	Insulin receptor substrate-2
PKB	Protein kinase B
TGF-β	Transforming growth factor-β
FFA	Free fatty acid
GLP-1	Glucagon-like peptide 1
PYY	Peptide-YY
GIP	Gastric inhibitory polypeptide
FXR	Farnesoid X receptor
TGR5	G protein-coupled bile acid receptor 5
AUC	Area under the curve
FGF-19	Fibroblast growth factor-19
GLP-1R	GLP-1 receptor
IL-1β	Interleukin-1β
NF-κB	Nuclear factor-κB

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Introduction

The global prevalence of diabetes and obesity in adults has increased in recent decades [1, 2], as the number of obese people increased from 105 million in 1975 to 641 million in 2014 [3]. Moreover, the International Diabetes Federation (IDF) showed that among adults aged 18–99 years in 2017, an estimated 451 million individuals had diabetes [1]. Thus, obesity-induced diabetes has become a social problem that urgently needs to be solved.

Currently, metabolic surgery is considered a standard treatment for obesity-related type 2 diabetes (T2D) [4–6], and the main benefits of surgery include weight loss and improved

glucose control. The traditional view of mechanisms underlying the effects of metabolic surgery includes the reduced daily caloric intake and various changes in gut hormones, which play crucial roles in regulating appetite, satiety, food intake, systemic metabolism, and insulin secretion. In addition, bile acid (BA) and the gut microbiota may also play roles in the effects of the surgery.

Both insulin resistance and impaired β-cell function are involved in the development of T2D [7]. Although it has been shown that islet function improves significantly after metabolic surgery, the mechanisms remain unclear. In this review, we focused on the effects of metabolic surgery, including Roux-en-Y gastric bypass (RYGB) and sleeve gastrostomy (SG), on islet function and the potential mechanisms.

Relationship Between Islet Function and Obesity or Diabetes

Insulin resistance and impaired β-cell function are the two causes of T2D [7]. In recent years, evidence has emerged linking immune cell infiltration into adipose tissue with chronic low-grade inflammation, and the latter plays a key role in the development of obesity-induced insulin resistance [8–10]. However, the prevalence of insulin resistance in the normal population is much higher than that in individuals with diabetes, suggesting that this condition is necessary for the development of T2D but not sufficient to cause the disease [11]. Insulin resistance in insulin-sensitive tissues could lead to increased insulin secretion from pancreatic β-cells [12, 13]. Activation of membrane-bound G protein-coupled receptors (GPCRs) enhances insulin secretion through the activation of protein kinase C (PKC) or the increase in cAMP, which activates protein kinase A (PKA) and potentiates Ca^{2+} influx [14, 15]. Increased pancreatic β-cell proliferation is caused by insulin receptor substrate-2 (IRS-2) signaling, inducing the phosphorylation of protein kinase B (PKB) and inhibition of the fork head-O transcription factor 1 [14, 16]. β-cells initially activate the compensatory pathway to improve the insulin secretion response, and the increased insulin secretion is initially sufficient to overcome the higher demand. However, owing to the increases in insulin resistance over time, depleted β-cells are unable to keep up with the increased insulin demand [8, 17, 18]. Ultimately, β-cells trigger some conditions that cooperatively promote β-cell dysfunction and death. Cellular pathologies such as oxidative stress, nutrient overload ("toxicity"), autophagy, and apoptosis can affect either islet function or β-cell mass [19, 20].

An evaluation of morphological parameters revealed that the reduction in the pancreatic α-cell areas in obese mice was associated with α-cell hypotrophy, increased apoptosis, and decreased proliferation [21]. This finding indicates that pancreatic compensatory adaptations that occur in the context of obesity might also involve pancreatic α-cells. Additionally, defects in α-cell function that occur together with obesity might be related to progression to diabetes.

Novel mechanisms and targets in β-cells can reveal potential methods for altering the natural progression of diabetes. A series of studies has attempted to identify targets to improve islet function, especially β-cell function. Intermittent fasting could preserve β-cell mass in obesity-induced diabetes via the autophagy lysosome pathway [22]. In addition, it could increase insulin secretion and glucose tolerance in individuals with T2D via inducing a shortage of free fatty acid (FFA)2 and FFA3 [23]. However, these findings are currently limited to animals, and their application in the clinical setting will require substantially more work. Some intervention drugs, such as glucagon-like peptide 1 (GLP-1) receptor agonists and anti-inflammatory drugs, can improve β-cell function and glucose control in a short time [24–29]. However, the limited clinical studies indicate that existing therapies do not prevent the progression of β-cell dysfunction in T2D, let alone reverse it; however, it is possible that metabolic surgery is an exception.

Potential Mechanisms of Metabolic Surgery in the Treatment of Obesity and T2D

First, food intake restriction and reduced daily caloric intake are believed to be important mechanisms underlying the effects of the surgery. In addition to RYGB, which is the gold standard metabolic surgery, SG can also offer the benefits of restriction and satiety [30–34]. This ability is the reason SG had clinical results, including weight loss and diabetes remission, similar to those of RYGB. Therefore, the main cause for weight rebound after metabolic surgery is the loss of restriction, and the aim of remedial surgery is to rebuild the restriction.

Second, changes in gut hormones are also a key factor underlying the effects of the surgery (Table 1). In RYGB, rapid food transport to the distal gut leads to surges in the release of the distal gut hormones GLP-1 and peptide-YY (PYY) [34, 35]. The responses of these two gut hormones, which have been suggested to play roles in both weight loss and T2D remission, have been called the 'fore gut theory' [36]. As some complex gut hormone changes are involved, SG is more than a restrictive bariatric surgery. The first difference is that ghrelin is markedly reduced after complete removal of the fundus, which produces the hormone ghrelin; this reduction increases weight loss [34–36]. Ghrelin levels are markedly suppressed following RYGB in some individuals [37], but this effect has not been observed in all studies [38, 39]. The second change is a rapid increase in postmeal GLP-1 and PYY responses caused by the rapid intestinal transit time after SG, which may contribute to weight reduction and metabolic improvement [34, 36]. Gastric inhibitory polypeptide

Table 1 Bile acid, microbiome, and intestinal hormone measures affected by the two major forms of metabolic surgery

	RYGB	SG
Bile acids	↑ Fasting, ↑ postprandial	↑ Fasting, ↑ postprandial
FGF-19	↑ Fasting, ↑ postprandial	↑ Fasting, ↑ postprandial
Change in microbiome	Yes	Yes
GLP-1	↑ Fasting, ↑ postprandial	No change fasting, ↑ postprandial
GIP	No change or ↓ fasting, ↓ Postprandial	No change fasting
Ghrelin	↓ or no change	↓
PYY	↑ Fasting, ↑ postprandial	↑ Fasting, ↑ postprandial

Data are derived from both human and animal studies. ↑ or ↑↑, increase or greater increase, respectively; ↓, decrease

(GIP) can increase insulin secretion depending on the glucose level and postprandial glucagon secretion. Some studies have demonstrated that the fasting GIP level is reduced 2 weeks after RYGB surgery in patients with diabetes [40, 41]. While postprandial GIP levels are reduced after RYGB [42], there is no change in fasting GIP levels after SG [43].

Third, a large amount of research in recent decades has focused on describing the potential of BAs in the metabolic improvements associated with surgery (Table 1). The level of BAs in circulation was found to change regardless of whether RYGB or SG was performed [44–47]. The G protein-coupled BA receptor 5 (TGR5) and farnesoid X receptor (FXR) signaling pathways, determined to be BA receptor-related pathways, are the central molecular foundation of the beneficial effects of metabolic surgery in animal models [48–50].

The last mechanism involved is related to the gut microbiota. Recent studies have shown that the gut microbiota of obese human beings is distinct from that of healthy individuals [51, 52]. Not surprisingly, metabolic surgery causes profound changes in the microbiome, likely a result of the dietary, environmental, systemic, and anatomical changes associated with metabolic surgery. In rodents, compared with sham controls, changes in the microbiome can be detected as early as 1 week after RYGB [53]. Similar patterns have been observed in humans following RYGB or SG [54–56].

Effect of Metabolic Surgery on Islet Function

As mentioned above, the pathogenesis of T2D involves both multiorgan insulin resistance and inadequate insulin secretion by pancreatic β-cells, leading to fasting and postprandial hyperglycemia. While the effect of metabolic surgery on diabetes remission is undeniable, T2D remission can occur only by improving the major metabolic defects, mainly involving pancreatic β-cells, that are involved in the pathogenesis of T2D.

Metabolic Surgery Can Significantly Improve Islet Function

Metabolic Surgery Improves β-Cell Function

The improvement of β-cells includes changes in quantity and function after surgery. In the aspect of quantity, animal studies have demonstrated that mouse pancreatic β-cells become dedifferentiated in response to hyperglycemia, reverting to a progenitor-like state [57–61]. In addition, pancreatic β-cells become dedifferentiated and convert to α- and "δ-like" cells in humans with T2D [62]. Interestingly, the dedifferentiated cells lie quiescent and can be redifferentiated to produce insulin, which can explain why restoration of β-cell function is possible years after the onset of hyperglycemia [63–65]. Increased pancreatic islet numbers and β-cell mass were observed after RYGB in the Goto-Kakizaki (GK) rat [66]. Simultaneously, there was a significant increase in the percentage of healthy endocrine cells, which was accompanied by a reduction in dedifferentiated pancreatic β-cells [67]. It should be stressed that these observations need to be made in humans, and moreover, the GK rat is not a good model for T2DM. These findings partly explain the recovery of β-cell function and glucose homeostasis in patients with type 2 diabetes following surgery.

On the other hand, the ability of pancreatic β-cells to secrete insulin in response to circulating glucose is critical for glucose homeostasis. RYGB and SG increase the rate of ingested glucose absorption into systemic circulation, increasing plasma glucose concentrations [31, 68], which impacts the rapidity and magnitude of the insulin secretory response to glucose or mixed meal ingestion. Most [69–77], but not all [78–80], studies found that the total postprandial (following glucose or mixed meal ingestion) insulin area under the curve (AUC) was significantly reduced after marked weight loss (15%) induced

by any type of metabolic surgery procedure. As insulin secretion is related to glucose levels and insulin sensitivity, a reduced AUC does not signify reduced β-cell function. In contrast, this concept suggests that β-cells switch from being excessively secreted to properly secreted after surgery. After minimal to moderate weight loss (10%), which occurs early after surgery, the total insulin response to glucose or mixed meal ingestion is usually decreased after RYGB [31, 80–82], whereas a decrease [31] or no change [79] is observable 1 week after SG (5–6% weight loss). This finding suggests that different types of metabolic surgery have inconsistent effects on β-cell function in the early stage. In addition, the shape of the insulin response curve depicts a fast increase in the insulin concentration after oral glucose or meal ingestion, a substantial insulin peak, and a steep decline after RYGB and SG. Moreover, some evidence has demonstrated that glycemic benefits, including changes in β-cell function [83], are independent of weight [84]. Above all, the improvement in β-cell function as a result of metabolic surgery is unquestionable.

Metabolic Surgery Effects the Function of Other Endocrine Cells in Islets

Although there was no change in the proportion of the α-cell area, RYGB could normalize glycemia by restoring not only insulin but also glucagon secretion in GK rats [85]. Pancreatic α-cells process proglucagon into glucagon, which suggests that the function of α-cells also improves after surgery.

Potential Mechanisms Underlying the Improvements in Islet Function

The exact mechanisms underlying islet function improvement after metabolic surgery have not yet been elucidated. We will explore the possible mechanisms related to the effects of reduced glucotoxicity and chronic inflammation, gastrointestinal hormones, and BAs on islet function after metabolic surgery (Fig. 1).

Effects of Reduced Glucotoxicity and Islet Inflammation on β-Cell Function

Generally, glucotoxicity refers to the slow and irreversible detrimental effects of chronically elevated glucose levels on β-cell function. Upon exposure of pancreatic islets isolated from obesity-induced diabetic mice to normal glucose concentrations, β-cells revert back to their typical morphology, and regulated insulin secretion is restored [86]. Upon intravenous glucose administration, an enhanced first-phase insulin response and improved HOMA-β were demonstrated in patients with T2D within 1 week after surgery, although these factors had not yet returned to normal [87]. This finding suggests that surgery has an early beneficial effect on β-cell function. The reduced glucotoxicity resulting from normalized glucose levels likely contributes to these changes.

Islet inflammation [24] contributes to hyperglycemia in patients with T2D. Pancreatic islets from patients with T2D are infiltrated with macrophages [88, 89], which release pro-inflammatory cytokines [90]. This finding is consistent with

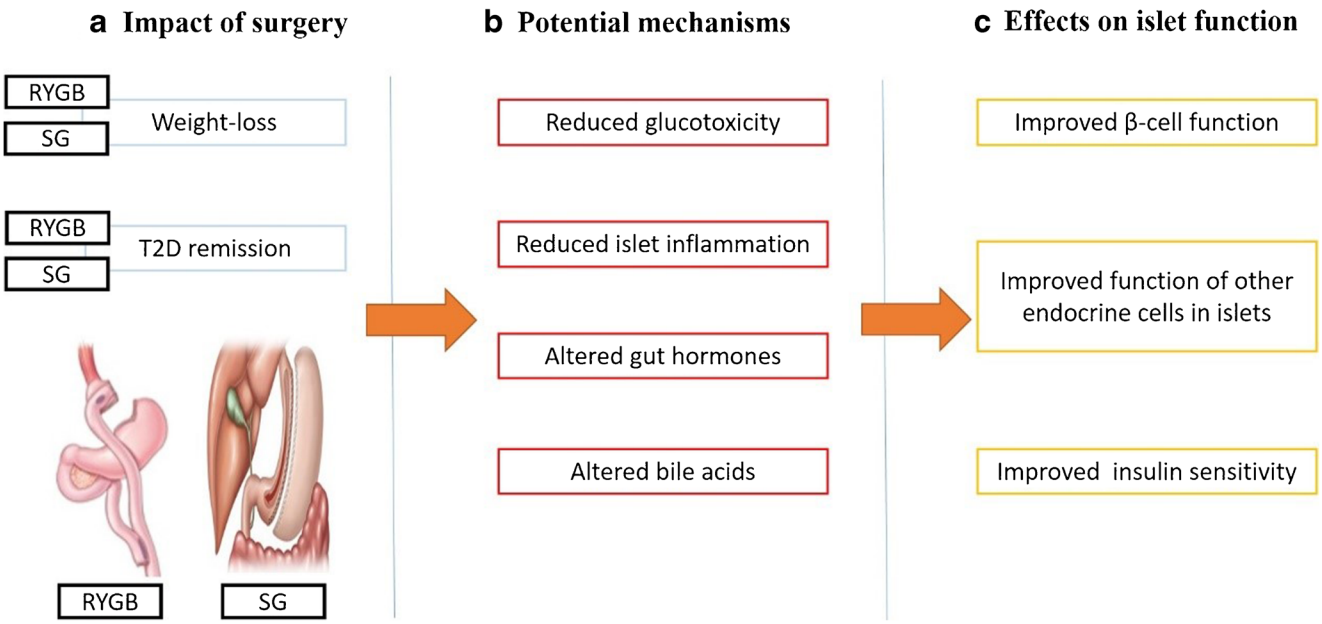

Fig. 1 Schematic of potential mechanisms contributing to improved glycemia after RYGB and SG. **a** Immediate effects of RYGB and SG. **b** Potential mechanisms involved. **c** Effects on islet function

reports of animals with T2D [88, 91–95]. These inflammatory mediators are known to compromise β-cell vitality and insulin production, and long-term exposure of human islets to hyperglycemia was shown to trigger the production of interleukin (IL)-1β and nuclear factor (NF)-κB by β-cells, which may coordinate autoimmune responses leading to β-cell apoptosis [96]. Numerous studies revealed that the levels of proinflammatory cytokines in patients who underwent metabolic surgery were reduced [97–101], indicating that chronic inflammation was improved in postoperative patients. This finding may imply that reducing islet inflammation improves β-cell function and preserves β-cell mass following metabolic surgery; this implication requires further research.

Effects of Gastrointestinal Hormones on Islet Function

The gastrointestinal hormone levels in patients with diabetes are markedly altered after metabolic surgery. In this section, we will focus on the effects of GLP-1 and PYY on islet function, which showed a significant increase after metabolic surgery [34–36].

Effects of gastrointestinal hormones on β-cell function GLP-1 has been shown to increase glucose-dependent insulin secretion, insulin synthesis, β-cell proliferation, and insulin sensitivity while inhibiting hepatic glucose production, β-cell apoptosis, and glucagon secretion and slowing gastric emptying, and, consequently, the rate of nutrient absorption [102]. After metabolic surgery, including SG and RYGB, the postprandial increase in GLP-1 from L cells of the small bowel acts as an incretin signal in the pancreas, increasing insulin secretion from pancreatic β-cells [102] and allowing the first-phase insulin response to be restored.

However, in genetic loss-of-function experiments involving mice lacking the only identified receptor for GLP-1, both SG and RYGB result in identical glucose improvements compared with those in wild-type mice, implying that activation of the GLP-1 receptor does not contribute to the benefits on islet function [103, 104]. Hence, increased GLP-1R signaling contributes to improved β-cell function but does not fully explain the marked improvement in glycemic control achieved after metabolic surgery.

PYY is secreted in combination with GLP-1 by L cells and is also expressed in pancreatic islets [105, 106], but not in β-cells, in adult mice [106]. Although a role of PYY in regulating energy homeostasis has been firmly established in recent years [107], it is now becoming clear that PYY also regulates glucose homeostasis [108]. Interestingly, PYY is coexpressed with glucagon and somatostatin in α- and β-cells of the pancreas, respectively [109], suggesting that PYY may also play a role in the paracrine regulation of insulin secretion.

Accumulating evidence shows that PYY directly alters insulin secretion through its action on pancreatic islets. In particular, overexpression of PYY in mouse islets leads to improved glucose-mediated insulin responses as well as increased β-cell mass and increased islet number and size [110]. Consistent with this finding, PYY ablation in the gut and pancreas drastically disrupts the islet structure and decreases the β-cell mass, triggering marked impairments in insulin secretion. Importantly, the reduced β-cell mass and lack of insulin release were reversed by treatment with a long-acting PYY (1–36) analog [109]. Moreover, PYY stands out as the humoral factor that mediates the antidiabetic effects of RYGB and is also capable of restoring dysregulated glucose-induced insulin secretion in islets isolated from rats with severe diabetes [85]. Combined with the increase in circulating PYY levels after metabolic surgery, PYY appears to play an important role in improved β-cell function.

Effects of Gastrointestinal Hormones on Other Endocrine Cells in Islets As pancreatic α-cells may process proglucagon into not only glucagon but also GLP-1, postprandial GLP-1 may be partly derived from α-cells. A murine SG model was generated with an inducible β-cell-specific-GLP-1 receptor (GLP-1R) knockout mouse model to investigate the role of β-cell GLP-1R in islet function; this study revealed two concepts. First, the results support a paracrine role of α-cell-derived GLP-1 in the metabolic benefits observed after SG. Second, the results revealed a role of β-cell GLP-1R as a regulator of α-cell proglucagon processing [111]. These findings support the idea that GLP-1 plays a coordinating role in islets.

As the beneficial effects of surgery persist in rodents lacking both GLP-1 and its receptor [103, 112], a GLP-1-independent mechanism is thought to exist. RYGB was also shown to normalize glycemia in individuals with diabetes by restoring insulin and glucagon secretion, and the gut hormone PYY mediated this improvement [85]. This finding suggests that PYY might affect α-cells and thus improve islet function after surgery.

Effects of BAs on Islet Function

Circulating BA levels are increased in humans and rodents after RYGB and SG, correlating with improved glucose tolerance [44–47]. Similarly, circulating fibroblast growth factor-19 (FGF-19) levels are increased after RYGB and SG [113, 114]. The anatomical rearrangements after RYGB lead to the delayed mixing of BAs with ingested food and exposure of the ileum to digestate-free chyme, offering a plausible explanation for the increased circulating BA and FGF-19 levels. This notion is supported by the finding that ileal interposition, with increased BA exposure, leads to increased circulating BA levels [115].

Effects of BAs on β-Cell Function FXR controls the enterohepatic cycling of BAs by inhibiting hepatic BA synthesis and intestinal absorption, rendering FXR a major regulator of BA signaling in both the liver and intestines. This mechanism shows that unlike wild-type mice, $FXR^{-/-}$ mice did not maintain body weight loss or exhibit improved glucose tolerance after SG [48]. FXR is also expressed in pancreatic β-cells, and $FXR^{-/-}$ mice have reduced insulin levels [116, 117].

Activation of the intestinal FXR receptor leads to increased levels of circulating FGF-19 (FGF-15 in mice), which has important metabolic effects. Circulating FGF-19 reduces circulating glucose levels and improves glucose tolerance in obese mice independent of insulin secretion [118, 119]. Recently, using a minipig RYGB model, further insights into the potential mechanisms underlying this phenomenon were obtained [120]. The findings showed that the intestinal uptake of ingested glucose is blunted in the BA-deprived alimentary limb despite the intact expression of the sodium-glucose cotransporter-1. Consequently, this component may be critical for mediating the beneficial effects of BA metabolism following metabolic surgery. However, whether BAs are the primary stimulants of FXR signaling in pancreatic β-cells that lead to functional changes in insulin levels remains unclear.

Effects of BAs on Other Endocrine Cells in Islets Although it is unclear how BA affects islet function, the role of BA receptors, including TGR5 and FXR [48–50], has become increasingly significant. The glucoregulatory benefits of SG surgery were blunted in $Tgr5^{-/-}$ mice relative to those in $Tgr5^{+/+}$ mice, and metabolically beneficial shifts in the circulating BA profile after SG surgery were impaired in $Tgr5^{-/-}$ mice [50]. Recently, TGR5 receptors were identified on both pancreatic islet α- and β-cells [121, 122]. Activation of the TGR5 signaling pathway reprograms pancreatic α-cells to produce GLP-1 under hyperglycemic conditions with a GLP-1-mediated increase in β-cell proliferation and mass [123]. These results demonstrate that TGR5 activation can mediate the cross-talk between α- and β-cells.

Moreover, a recent longitudinal study revealed a biphasic increase in total fasting plasma BA levels post-RYGB [120]. The early peak, 1-month postsurgery, is due to bacterially derived secondary Bas, such as ursodeoxycholic acid. A later peak, 2-year post-RYGB, reflects increases in the primary and secondary BAs deoxycholic acid and glycodeoxycholic acid, respectively. Circulating FGF-19 increases, but not until several months postsurgery, after the more rapid metabolic improvements occur [120]. The early changes in ursodeoxycholic acid and its metabolites may contribute to early improvements in insulin sensitivity after RYGB. These findings suggest that BA and FGF-19 may also impact islet function after surgery, and their role in T2D remission may require a long time to clarify.

Conclusions

Based on the effect of obesity-induced diabetes on β-cells, metabolic surgery is the most effective therapy available for patients with T2D. In addition to the reduction in glucotoxicity and chronic inflammation following metabolic surgery, gastrointestinal hormones and BAs also play important roles in islet function improvements. Currently, some interventions, including GLP-1 receptor agonists and anti-inflammatory drugs, can temporarily improve islet function, leading to improved glucose control. The effect of BAs suggests that they may be a new target for improving glucose control, and numerous physiological and molecular processes that are altered by metabolic surgery are associated with concomitant significant elevations in circulating BAs. Whether all these processes are driven, or potentially modified, by BAs is unknown, but this area of study remains ripe for identifying novel and better therapies for obesity and diabetes. More research focusing on the mechanisms underlying the improvements in islet function following metabolic surgery is needed, and the findings can be applied to the clinical treatment of patients with obesity and T2D.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

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