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The state of art on the mechanisms of laparoscopic sleeve gastrectomy in treating type 2 diabetes mellitus

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Abstract

Obesity and type-2 diabetes mellitus (T2DM) are metabolic disorders. Obesity increases the risk of T2DM, and as obesity is becoming increasingly common, more individuals suffer from T2DM, which poses a considerable burden on health systems. Traditionally, pharmaceutical therapy together with lifestyle changes is used to treat obesity and T2DM to decrease the incidence of comorbidities and all-cause mortality and to increase life expectancy. Bariatric surgery (BS) is increasingly replacing other forms of treatment of morbid obesity, especially in patients with refractory obesity, owing to its many benefits including good long-term outcomes and almost no weight regain. The BS options have markedly changed recently, and laparoscopic sleeve gastrectomy (LSG) is gradually gaining popularity. LSG has become an effective and safe treatment for type-2 diabetes and morbid obesity, with a high cost-benefit ratio. Here, we review the mechanism associated with LSG treatment of T2DM, and we discuss clinical studies and animal experiments with regard to gastrointestinal hormones, gut microbiota, bile acids, and adipokines to clarify current treatment modalities for patients with obesity and T2DM.

Key Words: Obesity; Type-2 diabetes mellitus; Laparoscopic sleeve gastrectomy; Gastrointestinal hormones; Adipokines; Gut microbiota; Bile acids.

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Core Tip: Obesity and T2DM incidence are currently increasing, and these afflictions have become important global health issues. Bariatric surgery is safe and effective for treating obesity and T2DM. The precise processes associated with this treatment, however, are somewhat unclear. Here, we review associated findings with respect to gastrointestinal hormones, intestinal microbiota, bile acids, and adipokines involved in LSG (the most popular bariatric surgery) of T2DM patients.

INTRODUCTION

Obesity, a complicated chronic metabolic illness induced by excessive lipid accumulation, has replaced smoking as the leading cause of early mortality linked to lifestyle[1],[2]. More than one-third of all nations have experienced a two-fold increase in the frequency of obesity during the 1980s, and most countries still report an increasing trend[3]. In 2015, more than 700 million adults and children were globally reported to be obese[4]. Numerous disorders, including type-2 diabetes mellitus (T2DM), afflictions of the cardiovascular system, hyperlipidemia, chronic renal disease, sleep apnea syndrome, non-alcoholic fatty liver disease, osteoarthritis, and metabolic syndrome, are closely associated with obesity[5].

T2DM is a prevalent metabolic condition that can damage various physiological systems and is defined by glucose metabolism problems elicited by poor insulin production and decreased insulin sensitivity[6]. The pronounced global increase in obesity, which is a major driver of T2DM, has markedly increased T2DM prevalence[7]. In 2017, more than 460 million individuals worldwide, i.e., 6.28% of the

global population, suffered from T2DM[8]. Obesity and T2DM have developed into important public health problems that constitute a heavy burden for the affected patients.

In addition to regular lifestyle behavior adjustments and medication, laparoscopic sleeve gastrectomy (LSG) has been acknowledged by worldwide diabetic organizations as a potent treatment of obesity and T2DM[9]. Even though the advantages of LSG for treating obesity and T2DM are commonly known, the processes by which LSG influences T2DM *via* several mechanisms, in addition to weight reduction, are still not comprehensively understood. Treatments can be optimized when the mechanisms underlying these metabolic processes and their effects on T2DM are elucidated. In this review, we focus on changes in terms of gastrointestinal hormones (GHs), adipokines, gut microbiota (GM), and bile acids (BAs) after LSG treatment of T2DM.

1. DEVELOPMENT OF BARIATRIC/METABOLIC SURGERY AND OVERVIEW OF PROCEDURES

Since the first bariatric surgery (BS) was performed in 1952, advances have been achieved throughout the past 70 years[10]. BS was intended to help patients lose weight and thereafter maintain normal weight; however, its importance in treating obesity-related comorbidities, particularly T2DM, has increasingly become prominent in clinical practice[11]. To improve surgery results and reduce complication rates, bariatric surgeons continually upgrade and enhance their techniques, and current bariatric operations include vertical-banded gastroplasty, duodenal switch, jejunoileal bypass, biliopancreatic diversion, adjustable gastric banding, Roux-en-Y gastric bypass (RYGB), and sleeve gastrectomy (SG)[12]. Additionally, BS is mostly carried out through laparoscopy due to the advances of lumpectomy surgery.

The most frequently performed BS techniques are RYGB and SG[13]. SG, initially introduced by Prof. David Johnston in the early 2000s, is a more physiologic variation of gastroplasty, which is normally a restrictive treatment, by using a longer, less curved vertical gastric tube to reduce stomach capacity[14]. Despite their anatomical distinctions,

both treatments have been proven safe and effective for treating obesity and T2DM[15]. BS can markedly decrease all-cause mortality and enhance life expectancy in obese adult patients, compared to standard obesity therapy, as evidenced by long-term follow-up of a large sample population. In addition, individuals who are overweight and suffer from T2DM benefit more from this treatment than those who suffer from obesity only[16]. A long-term follow-up study of 146 patients approaching 10 years showed complete remission of T2DM after LSG in 72.2%, significant improvement in 25.1%, and no change in only 2.7%[17]. The treatment effect of LSG on T2DM in morbidly obese patients was the same compared to laparoscopic Roux-en-Y gastric bypass (LRYGB), as demonstrated by a meta-analysis containing 9 studies, in which the remission rates of T2DM were 82.3% and 80.7% for LRYGB and LSG, respectively[18]. In addition, a meta-analysis containing 33 studies with 4,109 patients showed that patients receiving LSG experienced more significant improvement or remission of diabetes than those receiving laparoscopic adjustable gastric banding (LAGB)[19]. A meta-analysis designed for 1108 adult subjects showed that the probability of T2DM mitigation after LSG was 61.4%, significantly higher than in the medication group (2.5%). Based on the above findings, the remission rate of T2DM after LSG was not significantly different from LRYGB but significantly higher than drug treatment and LAGB[20].

Surgeons performing BS and patients tend to choose LSG over other BS because of its lower risk of complications, compared to other surgical procedures; further, it is less invasive, preserves the body's original natural channels, and has better clinical outcomes. Currently, LSG is globally the most common bariatric surgery[21]. Between 2010 and 2018, the proportion of LSG among bariatric surgery techniques increased from 2% to 61%, whereas that of RYGB decreased from 55% to 17%[22]. According to the International Federation for Surgery of Obesity Global Registry, 83,3678 weight-reduction procedures were recorded globally in 2019; however, only 1% of individuals qualified for surgical reasons received surgical treatment[23],[24]. Thus, there is considerable room for expansion of bariatric metabolic surgery. Considering the advances in bariatric surgery options, we focus on the

mechanisms of LSG relieving T2DM. The remission rate of T2DM after SG is approximately 65%[25], and this process involves, for example, GHs, GM, BAs, adipokines, the nervous system, and other potential mechanisms that are addressed here.

2. GHS

2.1 Ghrelin

Ghrelin, also referred to as the "hunger hormone", is a peptide of 28 amino acids predominantly generated by gastric fundus X/A cells. During fasting, ghrelin expression increases, and it is reduced after eating[26]. Ghrelin regulates the energy balance, increases the sensation of hunger, stimulates growth hormone release from the hypothalamus and anterior pituitary, and stimulates food intake to facilitate the buildup of adipose tissue[27],[28]. Additionally, ghrelin increases muscle insulin resistance and controls peripheral glucose homeostasis by lowering glucose-stimulated insulin release[29],[30]. In extremely obese individuals, ghrelin prevents the appropriate inhibitory response to food intake and does not return to normal after losing weight without surgery[31],[32]. Kalinowski *et al*[33] found that glucose metabolism improved in obese patients with BS, with reduced ghrelin levels after LSG and increased levels after RYGB. The same outcomes were obtained in other long-term follow-up trials, with patients reporting a significant decrease in ghrelin levels after LSG[34]. Stoica *et al*[35] confirmed this finding in a study on Wistar rats showing that LSG markedly decreased the levels of circulating acylated ghrelin. The primary location of ghrelin production is removed through LSG, which may be the primary cause of reduced ghrelin levels post-surgery. This ghrelin decrease after LSG likely explains the subsequent glycemic improvement as ghrelin is associated with higher circulating insulin and glucagon levels[36]. However, in a study on ghrelin-deficient and wild-type mice, the responses to LSG resembled those after glycemic control, which implies that ghrelin may not be required to improve the glucose metabolism[37]. The studies

cited above concluded that LSG substantially affects ghrelin production but that this effect was not the single causative factor of postoperative T2DM remission.

2.2 Peptide tyrosine tyrosine (PYY)

As a member of the pancreatic polypeptide-fold family, PYY is a digestive hormone released after eating by the L-cells among intestinal endocrine cells of the distal ileum and colonic mucosa, and in rodents, it is considered a satiety signal[38]. PYY may also affect insulin sensitivity and glucose absorption by acting on Y2 receptors, and it may modulate insulin secretion by acting on islets[39]. Reduced PYY levels occur in obese people during fasting and after eating, possibly because PYY synthesis, release, or clearance is impeded[39]. Exogenous PYY has recently attracted attention as an anti-obesity agent that can reduce food intake, delay stomach emptying, and lower the glycemic index[40],[41]. Potential LSG-induced alterations of PYY levels are currently controversial. One prominent question is whether PYY levels change after LSG surgery. Most studies concluded that PYY is elevated due to LSG[42],[43],[44], whereas one study suggested that PYY secretion, although numerically increased, is not statistically different from baseline[45]; however, considering the small number of patients included in this study (only six cases), this may not be a general pattern. The other question is whether increased PYY is restored to its baseline levels within a certain period after LSG.

Arakawa *et al*[42] observed an increase in PYY 26 wk after surgery but not after 52 wk. Similar results were obtained in a different study, showing higher PYY levels immediately after surgery, which then decreased to baseline levels within one year[44]; PYY secretion did, however, continue to increase postoperatively and remained above baseline levels at 18 mo, according to Alamuddin *et al*[42]. In an animal study, non-obese diabetic Goto-Kakizaki (GK) rats that were subjected to LSG showed substantial improvements in glycemic control, a significant decrease in glycated hemoglobin, and an increase in diet-induced PYY[46]. Moreover, in diet- and streptozocin (STZ)-induced diabetic obese mice, LSG can increase PYY levels. Animals

subjected to surgery also show higher glucose tolerance and fasting insulin improvement, and their insulin secretion increases and peaks faster following glucose infusion[47]. Boza *et al*[47] additionally performed ileal transposition with LSG, and compound surgery resulted in a considerable reduction in food intake, increased PYY levels, and improved glucose tolerance in obese diabetic mice. Current research suggests that PYY levels are increased in mice and humans subjected to LSG, which is directly related to lower food consumption. Further fundamental research is required to determine whether a direct connection exists between higher PYY and better insulin release and glucose tolerance.

2.3 Oxyntomodulin (OXM)

OXM, like PYY, is produced by intestinal L cells. It participates in the control of satiety, influences the production of hydrochloric acid by gastric secretion glands, and exerts a biological activity similar to that of glucagon[48],[49]. OXM has not yet been linked to a particular receptor, but intriguingly, it affects glucagon-like peptide (GLP)-1 receptors in the hypothalamic arcuate nucleus[50]. Furthermore, it exhibits entero-insulinotropic effects and β cell-protecting qualities[51]. According to previous studies, OXM may boost energy expenditure and control blood glucose levels in obese people while suppressing appetite and reducing food intake[52],[53]. In obese individuals with T2DM, OXM combined with GLP-1 and PYY has been demonstrated to improve glycemia and body weight[54]. Few studies examined how BS affects OXM, particularly when the surgical strategy is restricted to LSG; thus, little is known about changes in OXM following LSG. Nielsen *et al*[55] reported that post-LSG patients exhibited increased OXM production, which was correlated with body weight and postoperative dietary preferences. After RYGB, weight reduction may be predicted by early postprandial OXM, according to a different study[56]. Laferrère *et al*[57] conducted oral glucose tolerance trials and found that peak OXM levels were considerably higher in the surgery group compared to the control diet group and corresponded with an increase in PYY. Further, OXM levels following RYGB surgery did not change while fasting. In mice, exogenous OXM

increases glucose-induced insulin secretion, energy expenditure, and weight loss[58]. This effect of OXM may be due to its impact on the GLP-1 receptor (GLP-1R) as it does not stimulate insulin secretion in GLP-1R-/- mice[59]. The effect of exogenous OXM on T2DM has been partly established, however, further research is needed to understand how it is affected by LSG and other types of BS. Intriguingly, two studies have revealed that OXM might be a predictor of weight reduction after bariatric surgery. We hypothesize that this impact may be associated with changes in dietary practice and satiety.

2.4 Cholecystokinin (CCK)

CCK was first described in 1982[60], and as suggested by its designation, it is a peptide hormone which can cause gallbladder contraction linked to the gastrointestinal system. According to recent studies, CKK receptors are expressed in the pancreas, central nervous system, gallbladder smooth muscle, and stomach mucosa[61]. CCK interacts with CCK-1 receptors in distinct areas of the hindbrain to signal satiety and decrease food intake[62]. CCK has also been linked to neurophysiological processes, including anxiety, sadness, pain, learning, and memory[63],[64]. It controls stomach acid production, reduces BA release, and impacts gastrointestinal motility in the gut[65],[66]. In aged mice, CCK expression in β cells increases the area of the pancreas and shields the cells from STZ-induced diabetes and apoptosis, demonstrating a protective impact on β cells[62]. Frequent ravenous hunger of obese patients may be explained by the fact that insensitivity of vagal afferent neurons to CCK is decreased which reduces the drug's impact on satiety[60]. CCK and associated peptide hormones can successfully be used as adjuvant therapy for treating T2DM and obesity[67]. In high-fat diet (HFD) mice, CCK analogs can lower caloric intake, reduce body weight, and increase insulin sensitivity[68]. Numerous studies have shown that LSG significantly affects the levels of circulating CCK, thus improving glucose homeostasis and improving homeostasis model assessment of insulin resistance (HOMA-IR)[69],[43]. Additionally, elevated CCK appears to inhibit sympathetic action and subsequently inhibits the intrarenal renin-angiotensin

system, producing a hypotensive effect[70]. LSG has a stronger CCK-increasing effect than RYGB; however, it seems to be associated with lower remission rates in T2DM patients[71]. According to current research, CCK has a favorable function in preserving glucose homeostasis in T2DM, and one potential explanation may be its protective effects on pancreatic β cells. In cases with obesity, the weight-reduction effect of CCK may be mediated by a response of the central nervous system that re-establishes normal satiety signaling and reduces food ingestion. However, as there is no clear correlation between the increase in CCK and frequency of remission of T2DM after BS, it is not entirely conclusive to explain T2DM by changes in it alone.

2.5 GLP-1

GLP-1 is considered the most "successful" peptide hormone currently available. It is predominantly produced by intestinal L cells, and is a fundamental compound of several T2DM and obesity medications and of novel medications currently under research[72]. Under physiological circumstances, ingested food (including carbohydrates, glucose, proteins, and BAs) stimulates L cells scattered throughout the epithelium to release GLP-1 into the blood at a rate corresponding to food absorption[73]. This hormone is important in coordinating postprandial glucose homeostasis. GLP-1 stimulates the release of postprandial insulin, and activation of GLP-1R in pancreatic β cells stimulates the release of insulin, which depends on plasma glucose levels[74]. When β cells perceive elevated plasma glucose levels and GLP-1 signals from the intestine, it enhances insulin release after glucose intake, which is also known as the intestinal proinsulin effect[75]. Meanwhile, GLP-1 prevents pancreatic α cells from releasing glucagon[76], and it regulates gastric emptying, thus influencing appetite and contributing to a sensation of satiety. GLP-1 contributes to the ileal brake, allowing nutrients to enter the duodenum at the same rate as absorbed in the small intestine[77]. By targeting GLP-1R in the brainstem or hypothalamus, GLP-1 decreases hunger and increases satiety, which is complementary to the effects of PYY; however, both originate from L cells[78],[79]. In T2DM, GLP-1 secretion is reduced, and the effect of entero-insulin

is diminished[80]. However, this may be a consequence of T2DM rather than an etiology because non-T2DM patients with elevated blood glucose show a marked decrease in GLP-1 Levels[81]. The study of Shehata *et al*[82] showed that in obese adolescents with T2DM, LSG significantly increased GLP-1 Levels in the early postoperative period (until six months after surgery). However, it did not produce the same effect during the late postoperative period (12 mo after surgery). Furthermore, the size of the antrum was not linked to higher GLP-1, better glucose control, or less insulin resistance, but to higher T2DM remission rates. Min *et al*[83] came to similar conclusions, as GLP-1 Levels were increased in the early stage after surgery, but this effect was not persistent. Significant reductions in glycosylated hemoglobin (HbA1c) and insulin resistance (IR) predict improvement of T2DM. Vigneshwaran *et al*[84] also found that LSG led to increased GLP-1 Levels six months after surgery in T2DM patients who were not morbidly obese, but they did not record GLP-1 Levels thereafter. Further, obese people without T2DM also showed low insulin sensitivity and high insulin levels in the blood, compared to healthy controls. After LSG intervention. patients showed higher insulin sensitivity and markedly higher GLP-1 Levels[85].

In contrast, Rigamonti *et al*[86] compared GLP-1 Levels before and after surgery and examined how food ingestion rates affected GLP-1 secretion. They found no significant difference in GLP-1 Levels, but they proposed that LSG would make patients less resistant to insulin. However, who underwent RYGB showed higher GLP-1 Levels, better β cell function, and a higher chance of remission from T2DM[87]. In an animal study, Darline Garibay *et al*[88] showed that SG helps better control glucose levels by improving β cell GLP-1R signaling and increasing glucose-stimulated insulin secretion. Li *et al*[89] suggested that improved glucose metabolism in GK rats with SG was caused by increased GLP-1 secretion, which was achieved by increasing the amount of GLP-1 in the plasma through increasing GLP-1 production in the jejunal and ileal mucosa.

Nevertheless, other studies suggest a different perspective. Pérez *et al*[90] used GLP-1R-deficient mice which after SG did not differ significantly from wild-type controls in terms of weight and body fat reduction, improved glucose tolerance, food intake, and

food preference. The authors concluded that GLP-1R activity was not required for SG to improve glucose metabolism and reduce body weight. Evidence from recent studies supports the notion that GLP-1 is crucial for maintaining glucose homeostasis, and the prospect of developing effective treatments is encouraging. As a hormone with an intestinal proinsulin effect, production of GLP-1 may be decreased during T2DM. The effect of LSG on GLP-1 currently prefers the ability of LSG to increase GLP-1 Levels in the early postoperative period. It may alter glucose homeostasis and help cure T2DM by boosting intestinal L-cell GLP-1 production and promoting GLP-1 signaling in pancreatic β cells. However, it remains controversial why SG produces the same surgical effect in mice, even without GLP-1R. Therefore, further studies are required to determine how GLP-1 influences glucose metabolism in T2DM after LSG.

2.6 GLP-2

GLP-2 consists of 33 amino acids and is encoded at the carboxyl terminus of the GLP-1 sequence in the glucagon gene. Like GLP-1, it is predominantly produced by enteroendocrine L cells in the ileum and large intestine[91]. It is produced in response to food stimulation in the gut, and GLP-2 is primarily responsible for inhibiting gastrointestinal motility and intestinal nutrition (enhancement of intestinal growth, digestion, absorption, barrier function, and blood flow)[92]. Due to its distinct intestinal nutrition effects, the use of GLP-2 analogs for the treatment of intestinal failure can markedly reduce the frequency of required parenteral nourishment[93]. GLP-2 contributes to preserving the energy balance, and in particular, it promotes nutritional absorption in the gastrointestinal system; this is achieved not only by enterotropic action but also by decelerating gastrointestinal motility, which extend the duration of nutrient digestion and absorption. Intriguingly, GLP-2 is a peptide hormone that has been associated with anorexia[94]. Its receptor, GLP-2R, is expressed in the brainstem, hippocampus, and hypothalamus, which are thought to be essential for maintaining homeostasis of energy[95]. Peripheral GLP-2 injection decreases food intake in mice on the short term[96].

Furthermore, mice with a specific GLP-2R deficiency in proopiomelanocortin neurons show increased plasma insulin and hepatic glucose production as well as glucose intolerance[97]. Moreover, endogenous GLP-2 demonstrated a protective effect against insulin resistance in HFD mice[98]. Romero *et al*[99] observed an increase in GLP-2 Levels and an improvement in glucose tolerance in the first postoperative phase after LSG. Cummings *et al*[100] attained similar outcomes in an animal experiment, where SG enhanced glucolipid metabolism and postponed the development of diabetes in UCD-T2DM rats, in addition to increasing GLP-2 Levels. GLP-2 regulates the circulating BAs, although Patel *et al*[101] showed that it is not required for body weight and glucose homeostasis in GLP-2 receptor-deficient SG mice. However, Patel *et al*[101] also found that GLP-2 regulates circulating BAs, but it is not required for body weight and glucose homeostasis in GLP-2R-deficient SG mice. In conclusion, in-depth research on GLP-2 is lacking, and data to determine how LSG affects GLP-2, particularly in humans, are currently insufficient. The available data merely provide evidence for the hypothesis that the observed increase in GLP-2 Levels after LSG is likely to play several functions in homeostatic processes in vivo, whereas the precise mechanisms remain unknown.

2.7 Glucose-dependent insulinotropic polypeptide(GIP)

Following food ingestion, endocrine K cells in the crypt-villi axis produce GIP, a protein comprising 42 amino acids. This hormone was originally designated gastric inhibitory polypeptide because of its capacity to reduce stomach secretion and motility[102]. However, GIP was then identified as an incretin hormone capable of enhancing glucose-dependent insulin secretion from pancreatic β cells and thus received its current designation[103]. GIP exerts two functions. As a sister hormone of GLP-1, GIP exerts the same proinsulin action, and the loss of effects of entero-functional insulin is the primary cause of poor postprandial glycemic control in T2DM[104]. GIP agonists have been developed for the treatment of T2DM and obesity[105]; however, it is crucial to note that GIP agonists do not effectively reduce blood sugar levels in T2DM; nevertheless, when coupled with GLP-1 and GIP agonists, their benefits are

significantly larger than those of GLP-1 alone[106]. GIP, by contrast, may influence the distribution of fat in adipose and non-adipose tissues, causing ectopic fat deposition and stimulating the accumulation of visceral and hepatic fat[107]. The major source of circulating non-esterified fatty acids is visceral fat, and a persistent increase in these acids is linked to the development of insulin resistance and T2DM[108]. Additionally, inflammation of pro-inflammatory adipokines and adipose tissue may be exacerbated by GIP[109]. Excessive GIP production contribute to the development of fatty liver and non-alcoholic fatty liver disease (NAFLD)[110]. GIP receptor antagonists may restore obesity, IR, and related metabolic problems in mice caused by prolonged HFD intake, thus they are also a viable treatment option[111]. According to one study, GIP level of patients increased linearly following LSG and continued to increase for four years, resulting in better glycemic management[83]. A study by Romero *et al*[99] on extremely obese individuals revealed an elevated GIP response following LSG, whereas after RYGB, no comparable reaction was observed. Other results suggest that RYGB reduces postprandial GIP secretion, owing to restricted food transit through the duodenum and jejunum[112]. In STZ-induced diabetic mice, Wang *et al*[113] found no change in GIP between SG- and sham-operated groups, and SG had no mitigating impact on STZ-induced diabetes. GIP seems to exert contrary functions in obese T2DM patients. However, this hormone belongs to the enterotrophic insulin family, and its agonists may be utilized to treat T2DM and obesity, resulting in hypoglycemia and weight reduction benefits. By contrast, it has been shown to enhance adipose inflammation, induce fat deposition, and to be linked to the onset of fatty liver and NAFLD. With regard to how BS may affect GIP, LSG seems to raise GIP levels, whereas RYGB causes a decrease in GIP production, depending on the surgical method. Given that GIP exerts contrasting functions, currently available studies cannot conclusively determine whether changes in GIP secretion after LSG are advantageous or harmful.

2.8 Gastrin

Gastrin is produced in the G cells of the gastric sinus and duodenum, and it is released in response to stimulation by the vagus nerve and gastrin-releasing peptide[114]. This hormone family comprises numerous peptides, with varying levels of biological activity and lengths[115]. The primary roles of gastrin include inducing gastric acid production in the stomach *via* a Ca-dependent release mechanism, acting on intestinal chromophobic cells in the fundus to trigger histamine release, stimulating the development and motility of the gastric mucosa, and suppressing hunger[116]. Recent studies focused on the relationship between gastrin and the onset and progression of gastrointestinal cancers, particularly neuroendocrine tumors[117]. IR and abdominal obesity are correlated with low gastrin levels[118]. Gastrin and GLP-1 dual agonists exert immunomodulatory effects that enhance insulin levels and β-cell mass in non-obese diabetic mice, eventually improving glycemic control. Furthermore, in individuals with T2DM, the addition of proton pump inhibitors (PPI) to glucose-lowering medications markedly raised gastrin levels, enhanced β cell activity, and reduced HbA1c levels[119],[120],[121]. A trend towards increased gastrin secretion after SG was observed in female patients who had undergone BS compared to patients receiving a protein-rich meal mix. However, no statistically significant difference was observed, while gastrin was significantly lower after RYGB. Notably, a negative correlation occurred between gastrin secretion and glucose levels after SG[118]. Grong *et al*[122] found that SG had superior effects in inducing hypergastrinemia, lowering HbA1c, and improving glycemic control in a GK rat model. In a subsequent study, the authors assessed the -cell mass in GK rats using three-dimensional optical projection tomography, showing that -cell mass was maximally preserved after SG, which may be related to high gastrin levels and long-term improvement in glycemic parameters following surgery[123]. Grong *et al*[124] also suggested the presence of circulating high gastrin in GK rats after SG. However, this was similar to the result after PPI intervention, with no difference in glycemic control between the two groups, and SG did not improve β cell mass. Few human studies on gastrin changes after SG are available, and current evidence suggests the presence of high gastrin levels after SG,

which may have a positive effect on glycemic control in T2DM; however, the precise mechanisms involved are unclear. In general, the results are inconsistent as to whether high gastrin improves β cell quality.

2.9 Fibroblast Growth Factor (FGF) 19 and FGF 21

At least 22 protein family members of FGFs are associated with angiogenesis, wound healing, metabolic control, and cell growth, development, and migration differentiation[125]. The majority of these work as paracrine or autocrine factors. FGF19, FGF21, and FGF23 are hormone-like members of the FGF family and have certain structural characteristics that facilitate endocrine effects[126]. FGF19 is produced in the brain, gallbladder, and distal small intestine. It inhibits hunger and regulates BA and nutrition metabolism, glucose and lipid metabolism, energy expenditure, and obesity[127]. FGF21 controls lipid and carbohydrate metabolism, elicits white adipose tissue (WAT) thermogenesis and browning, indirectly increases insulin synthesis in the pancreas, improves insulin sensitivity, and decreases food intake[128]. FGF23 is a hormone produced by osteoblasts and osteoclasts in the skeleton and is primarily involved in mineral metabolism to control phosphate levels[129]. According to several studies, there is a significant increase in FGF19 following SG, and this increase is linked to better glycemic control and reduced systemic inflammation[130],[131],[132]. Yang *et al*[133] observed an increase in FGF19 in VSG but no changes in RYGB. A meta-analysis revealed an increase in FGF19 and a negative correlation between FGF19 and BMI after SG[134]. Huang *et al*[135] noted that higher FGF19 Levels and reduced BA levels after SG may play a role in T2DM remission and NAFLD improvement; they also hypothesized that low preoperative FGF 19 Levels may predict improvement of NAFLD.

With respect to FGF21, Khan *et al*[136] found a link between elevated FGF21 and weight loss after SG, indicating that FGF21 may play a part in the postoperative energy balance. By contrast, Nielsen *et al*[137] did not detect changes in FGF21 after SG, and FGF21 Levels were not related with food choice. FGF19 Levels were decreased and FGF21 Levels were increased in obese patients, and FGF21 Levels further increased

when obese patients showed T2DM. SG increased FGF19 Levels while decreasing the unnaturally increased FGF21 Levels. The authors concluded that FGF19 Levels were mostly related to physical obesity, particularly visceral obesity, whereas those of FGF21 were primarily linked to glucose homeostasis[138]. Yen *et al*[139] confirmed this and further observed a substantial decrease in FGF21 Levels after SG and a strong positive association between FGF21 and C-peptide, insulin, and the homeostasis model evaluation of the postoperative IR index.

In conclusion, the available studies are in line with our findings that FGF19 is typically elevated in the postoperative period and that it may control the release of BAs to produce its effects. The elevation of FGF19 after SG is not specifically correlated with T2DM but is linked to a decrease in the body weight index. Contrarily, FGF21, which is frequently increased in obese patients with T2DM, has an independent function in obesity and is linked to metabolic syndrome, hyperinsulinemia, onset of diabetes, aberrant glucose metabolism, and IR[140]. Due to its potential to ameliorate the FGF21 increase induced by obesity or T2DM, SG may play a significant part in preserving glucose homeostasis. FGF21 should be further studied, and it may be a more important metabolic marker of illness in T2DM than FGF19.

Overall, the control of different components of the gut-brain axis, the gut-adipose tissue axis, the gut-liver axis, the gut-pancreatic axis, and the gut-muscle axis all play a role in the overall complexity of the gastrointestinal hormonal alterations after LSG. The surgical method used in RYGB (partial removal of the small intestine and stomach) may explain endocrine differences between LSG and RYGB; this also suggests that the two treatments affect T2DM differently because of such discrepancies. Although the benefits and drawbacks of the two approaches are not entirely clear, one may infer from the few available data that the potential of LSG ability to relieve T2DM is connected to gastrointestinal hormones, which may result from systemic rather than specific hormonal alterations.

3. ADIPOKINES

Adipose tissue is divided into WAT and brown adipose tissue (BAT), classically considered a long-term storage organ that releases free fatty acids to meet the body's energy requirements during fasting or thermoregulation and has a mechanical protective impact on internal organs[141],[142]. According to current studies, adipose tissue is one of the major endocrine organs in the body and plays a significant role in systemic homeostasis[143]. Adipocytes are metabolically active, and they are effective secretory cells that can release large quantities of adipokines. Adipokines may influence several biological processes, including appetite regulation, inflammatory and immune functions, glucose and lipid metabolism, cardiovascular homeostasis and reproduction, and other essential physiological processes[144]. This review focuses on T2DM and obesity; hence, other physiological functions will not be described in any great detail. Leptin, adiponectin, resistin, and vaspin are adipokines associated with glucose metabolism. Insulin sensitivity is linked to leptin, adiponectin, chemerin, and omentin, whereas IR is associated with apeline and nesfatin-1. By contrast, leptin and vaspin are also important in controlling appetite[145],[146]. As a result, T2DM and adipokine changes are tightly associated in obese people. Below, we provide more details on how LSG affects specific adipokine metabolism processes and its potential impact on T2DM and also summarize the approximate mechanism in Figure 1.

3.1 Leptin

Leptin has a tertiary structure of a globular protein, comprising 167 amino acids. It is predominantly synthesized in white adipose tissue, and primarily acts on trans-modal receptors to exert its effects[147]. Food consumption, systemic adiposity, and hormones affect the amount of leptin that is secreted, with insulin playing a significant regulatory role[148]. Prolonged hyperinsulinemia leads to an increase in circulating leptin concentration[149]. Considering the IR status of obese patients, high leptin levels are likewise a characteristic of obesity. Leptin thus controls hunger, satiety, food intake, and energy use[150].

Meanwhile, it may play an insulin-sensitizing role and is an important regulator of β cell mass and survival. Recombinant leptin has been established for obesity treatment based on its various important physiological roles. However, little progress has been made, which may be due to long-term leptin-resistance during obesity[151]. When such resistance is reduced, recombinant leptin treatment produces effective weight reduction and glycemic control[152]. Thus, studying the alterations in leptin that occur after LSG and how they affect T2DM and obesity is crucial. Numerous studies have produced similar findings, and the impact of LSG on leptin is generally beneficial, with a discernible decrease in leptin levels after surgery that remained throughout long-term follow-up[34],[153],[33]. Mazahreh *et al*[154] concluded that LSG increased the expression level of leptin receptors, which alleviated leptin resistance. Leptin levels and IR were correlated in patients, and pre-LSG leptin levels were predictive of IR, according to Hany *et al*[155]. Additionally, Arble *et al*[156] also reported that SG improves ventilatory drive in patients with sleep apnea through a leptin-dependent mechanism. Stoica *et al*[35] showed that SG decreased leptin expression in mice. Similarly, Du *et al*[157] discovered that SG lowered leptin expression in HFD-fed mice, which caused translocation of glucose transporter protein 2; resulting in inhibition of intestinal glucose absorption. In leptin receptor-knockout mice, long-term weight reduction following SG was shown to require the action of leptin; however, the improvement in blood glucose does not seem to depend on leptin. The authors concluded that a significant improvement in blood glucose caused by SG through enhanced insulin sensitivity, independent of reduced feeding and weight loss[158]. LSG has a well-documented impact on lowering circulating leptin levels and enhancing leptin resistance, and these beneficial effects have been linked to several healthful physiological processes. However, it remains controversial whether changes in leptin levels have beneficial effects on glucose metabolism in T2DM, which may be involved partly by reducing glucose uptake and improving insulin resistance, among other effects. The role of leptin in this process is not all or nothing, but good or better.

3.2 Adiponectin

WAT secretes adiponectin, one of the most prevalent adipokines in the bloodstream of humans[159]. As a secreted protein, it functions by interacting with the cell membrane receptors adiponectin receptor (AdipoR) 1 and AdipoR2. AdipoR1 is primarily expressed in liver and skeletal muscle tissue, and AdipoR2 is predominantly expressed in the liver[160]. Adiponectin increases skeletal muscle glucose absorption and fatty acid oxidation, thus inhibiting gluconeogenesis in the liver[161],[162]. Additionally, adiponectin has anti-diabetic properties and activates the AMP-activated protein kinase (AMPK) pathway, which interacts with the AdipoR1 receptor to elicit insulin sensitization[163]. Furthermore, lipocalin exerts anti-inflammatory effects, it is linked to the onset of atherosclerosis, and it effectively inhibits the activation of the nuclear transcription factor-kappa B (NF-kB) pathway and production of the NF-kB nuclear protein p65[164]. Obese patients with T2DM exhibit reduced adiponectin levels which are associated with increased expression of pro-inflammatory cytokines; this may also be associated with low-grade chronic inflammation[165]. According to previous studies, increasing the amount of lipocalin in the blood would be a viable therapeutic approach to treat disorders caused by obesity. Thiazolidinediones, which act as peroxisome proliferator-activated receptor γ (PPAR-γ) agonists, may raise adiponectin levels and successfully regulate blood sugar. However, their applicability is more constrained owing to lower safety (with adverse side effect including hepatotoxicity, heart failure, edema, and reduced bone density)[166]. Lopez-Nava *et al*[167] reported increased adiponectin levels after LSG, no equivalent changes were seen after endoscopic SG, and patients exhibited increased weight loss following LSG. Rafey *et al*[168] obtained similar results with increased circulating adiponectin after LSG, and the authors suggested that the leptin-to-adiponectin ratio was correlated with improved insulin sensitivity and weight loss, and that this ratio decreased significantly after surgery. Natalja *et al*[169] took an identical perspective: adiponectin levels increased after BS, however, the authors did not distinguish between various surgical techniques. In GK rats, SG increased serum adiponectin and adipose tissue PPAR-γ expression, decreased IR, and enhanced

adipose tissue health and angiogenesis[170]. Adiponectin may have a role in improving glucolipid metabolism and delaying the development of T2DM in UCD-T2DM mice when SG is performed[100]. In addition, a combination of SG and partial small bowel resection resulted in elevated adiponectin levels, which may contribute to improved glucose homeostasis[171]. Adiponectin exerts a significant role in glucose metabolism, whether in patients with T2DM, obesity, or both. Elevating the circulating adiponectin levels through medication seems to be an effective option; however, this treatment modality should be considered with caution regarding the aspect of safety. The effect of LSG on adiponectin is currently presumed consistent, with a postoperative increase, which may be one of the mechanisms by which LSG can help treat T2DM and obesity. Risks and safety of LSG are manageable for specialist weight loss metabolic surgeons, which is one of its advantages over established pharmacological approaches.

3.3 Apelin

Apelin is a late-discovered adipokine peptide with multiple active isoforms. Its receptor, APJ, is an extensively distributed G protein-coupled receptor[172]. Various tissues and cells in the human body contain apelin/APJ, which perform various physiological tasks, including controlling food intake, cell proliferation, and angiogenesis[173]. Apelin is recognized as a helpful adipokine and, like adiponectin, is thought to be an insulin sensitizer[174]. Exogenous apelin supplementation is still beneficial for IR and for the glucose metabolism, even when endogenous apelin levels are high in obese patients and those with T2DM[175]. Exogenous apelin has been shown to improve insulinotropic activity, adipocyte glucose absorption, and insulin release in obese mice, and it is similarly beneficial in human patients[176],[177]. Soriguer *et al*[175] reported a significant decrease in apelin levels in morbidly obese patients with impaired fasting glucose or T2DM due to BS. Apelin levels were significantly positively correlated with changes in serum glucose and negatively correlated with insulin sensitivity. Arica *et al*[178] observed that laparoscopic gastric banding reduced elevated apelin levels in obese morbidly obese patients. However, we were unable to identify

studies on the effects of LSG on apelin. As a novel therapeutic target and important biomarker for metabolic illnesses, including diabetes and obesity, the apelin/APJ signaling pathway has recently attracted attention. However, few studies on apelin and BS are available, and they suggest that apelin levels decrease postoperatively, which seems to be disadvantageous.

3.4 Nesfatin-1

The novel adipokine nesfatin-1 is not only released by adipose tissue, but its synthesis and secretion have also been observed in central nervous tissues including the hypothalamus[179]. So far, the nesfatin-1 receptor remains unknown; however, specific binding sites have been found in the central nervous system, gastrointestinal tract, and pancreas[180]. Nesfatin-1 is considered an efficient anorexigenic peptide with regulatory effects on energy metabolism through reducing food intake[181]. Nesfatin-1 expression is lower in obese people, and its levels are negatively correlated with body mass index, weight, and adiposity[182]. Similar observations were made in T2DM patients, whose nesfatin-1 Levels were lower than those of healthy subjects or T1DM patients[183]. Nesfatin-1 stimulates insulin secretion, increases proinsulinogen mRNA expression, and has antihyperglycemic effects during glucose metabolism[184]. A previous study showed that supplementation with exogenous nesfatin-1 elicited resistance to hyperglycemia in mice, suggesting that nesfatin-1 may be a potential therapeutic target for T2DM[185]. According to several studies, LSG raises postoperative nesfatin-1 Levels in patients. Nesfatin-1 has been linked to a reduction in postoperative appetite, according to Dogan *et al*[186], whereas Yang *et al*[187] observed a link between nesfatin-1 and NAFLD. Lee *et al*[188] demonstrated that nesfatin-1 decreased after SG or RYGB, and they proposed a link between nesfatin-1 and glycemic control.

In contrast, Majorczyk *et al*[189] came to the exact opposite conclusion, suggesting that LSG decreases nesfatin-1 Levels and that there is no significant correlation between nesfatin-1 and improvement in body weight or glucose metabolism. There is a controversy with regard to LSG's impact on nesfatin-1, with starkly contrasting

opinions. The correlation between nesfatin-1 and weight, appetite, and hepatic steatosis after LSG has been demonstrated, however, only one study has shown a correlation between nesfatin-1 and glycemic control after LSG. Thus, nesfatin-1 may play a minor role in the LSG-mediated remission of T2DM.

3.5 Resistin

Resistin is a specific adipokine specifically expressed and secreted by adipose tissue[190]. Its effects involve endocrine, autocrine, and paracrine mechanisms, however, its receptor is unknown[191]. Resistin is considered a connection between obesity and T2DM as it reportedly opposes the action of insulin and interferes with glucose homeostasis in vivo, which results in the progress of T2DM[192]. Resistin is also a pro-inflammatory regulator of macrophages, peripheral blood mononuclear cells, and vascular cells, with pro-inflammatory actions and higher expression during pathological states of inflammation, according to recent studies[193],[194]. Resistin levels were positively correlated with insulin resistance in T2DM patients with hyperresistinemia and in obese people, according to a meta-analysis of 20 studies. However, no such association was found in patients with normal resistin levels[195]. A study showed that leptin and resistin levels decreased following LSG, and liver histopathology results improved[196]. Similar observations were made in a different study, which concluded that weight reduction after LSG was associated with altered levels of anti-inflammatory adipokines and better glucose metabolism[197]. Šebunova *et al*[169] observed that resistin was markedly higher after LSG than after RYGB, however, the decrease from the preoperative period was not significant. Farey *et al*[198] found that postoperative resistin levels exhibited a reducing trend which was not statistically significant, and that resistin levels of obese patients were lower than those of non-obese controls.

Additionally, a meta-analysis revealed that weight reduction surgery had no pronounced impact on resistin levels[199]. Presently available studies seem not to support the hypothesis that LSG regulates resistin levels to facilitate T2DM remission. However, the various limitations of such studies should be considered, particularly

with regard to small sample sizes and the fact that resistin is not consistently highly expressed in obese people. Further research is required to determine whether preoperative resistin levels are generally within a normal range to more accurately assess its impact on T2DM.

3.6 Chemerin

Chemerin was found to be highly expressed in human WAT in 2007. Chemerin is a novel adipokine that binds to the orphan G protein-coupled receptors chemokine-like receptor (CMKLR) 1, chemokine (C-C motif) receptor-like (CCRL) 2, and G protein-coupled receptor (GPR) 1 to exert its potential autocrine and paracrine effects [200],[201]. It may have a role in energy balance and metabolism *in vivo* and is linked to adult obesity, T2DM, and metabolic syndrome, according to recent research[202]. Most respective studies found that people with poor glucose homeostasis had higher serum chemerin levels and that this increase was inversely linked with glycemic control parameters[203]. A meta-analysis suggested a marked decline in chemerin levels after BS, however, various surgical methods were not distinguished[199]. Terra *et al*[153] reported a significant decrease in chemerin 12 mo after LSG, compared with the baseline levels, in a pattern similar to that after RYGB. Similar findings were reported by Jouan *et al*[204], who discovered a decrease in chemerin after surgery and suggested that chemerin may be utilized as a predictor of a postoperative inflammation; however, the changes in chemerin after LSG were not uniform. The findings of Ctoi *et al*[205] did not reveal any significant differences in chemerin six months after LSG. Chemerin is a relatively novel adipokine; thus, little information is available, and most conclusions originate from meta-analyses. Fundamental research is thus required to understand the mechanisms of action of chemerin acts, particularly with regard to T2DM. The limited available data do not support a link between chemerin and improved glucose metabolism after LSG.

3.7 Omentin-1

Omentin-1 is the primary circulating form of omentin, also referred to as intelectin-1, which is mainly expressed in visceral adipose tissue and exerts endocrine effects resembling those of hormones[206]. Omentin-1 increases insulin sensitivity, which is key in maintaining the body's metabolism. In addition, it also has anti-inflammatory properties through the intracellular Akt/AMPK/NF-B and mitogen-activated protein kinase (MAPK) signaling pathways[207]. Glucose/insulin and FGF21 affect how omentin-1 is regulated, with glucose/insulin decreasing its expression and secretion and FGF21 increasing it[208],[209]. Omentin-1 expression profiles of obese and T2DM patients showed that its expression and secretion were suppressed in patients suffering from obesity[210], T1DM[211], T2DM[212], and metabolic syndrome. In addition, the chromosomal area of omentin-1 is linked to T2DM in certain groups. Thus, this gene may be associated with T2DM susceptibility[213]. Increased circulating omentin-1 Levels and decreased fecal omentin mRNA after LSG may contribute to surgery-induced metabolic improvement and weight reduction[214]. Sdralis *et al*[215] proposed that LSG combined with omentotomy reduced the expression of omentin-1, but LSG alone increased it, and a low-calorie diet had no significant effect on omentin-1. The pattern of omentin-1 expression after LSG is intriguing, however, as omentin-1 is influenced by glucose/insulin and FGF21, it is unclear whether the reduction in blood glucose under T2DM remission would prevent the inhibition of omentin-1, causing it to increase, or whether the higher omentin-1 levels affected T2DM remission. Omentin-1-based medication may be an emerging option for treating obesity and T2DM, considering the link between omentin-1 and IR. However, the mechanisms of action of omentin-1 during surgical operations are unclear.

3.8 Visfatin

Visceral fat secretes the adipokine visfatin, which has effects similar to those of insulin[216]. Visfatin interacts with insulin receptors during gluconeogenesis to increase glucose absorption in liver and muscle tissue, thus lowering blood sugar levels[217]. Further, it supports the effects of insulin by causing the phosphorylation of insulin

receptors 1 and 2[218]. Additionally, the autocrine activity of visfatin in the liver enhances insulin sensitivity[219], and it also works on the hypothalamus in the center to influence insulin release and reduce IR[220]. According to studies, visfatin contributes to IR and T2DM in a dose-dependent manner, and obese patients with T2DM showed higher intraserum levels of visfatin than obese patients without T2DM[221]. However, only few studies could be identified that examined how LSG affected visfatin, one of which found no evidence of a substantial change in visfatin after LSG[222]. Similar conclusions were drawn in a meta-analysis, which showed that BS had no marked impact on visfatin expression or secretion[195]. Animal experiments produced similar results[223]. Visfatin has a beneficial effect on T2DM or decreased glucose tolerance because of its insulin-like activity. However, uncertainty remains regarding how LSG affects visfatin levels and how visfatin contributes to T2DM remission following LSG.

3.9 Retinol binding protein 4

Retinol binding protein 4 (RBP4) is an adipokine secreted by WAT. The primary function is to transport retinol, the active metabolite of vitamin A, from the liver to target tissues. High levels of RBP4 are associated with developing metabolic diseases such as obesity, insulin resistance (IR), metabolic syndrome, and T2DM[224]. In obesity, abnormal levels of RBP4 produce both local and systemic effects (retinol homeostasis and transport in vivo)[225]. It exacerbates the inflammatory state in obesity *in vivo* by activating Toll-like receptor (TLR) 2 and TLR4/myeloid differentiation protein 2 receptor complexes in macrophages[226]. In T2DM, RBP4 is associated with insulin resistance and the progression of several T2DM co-morbidities, such as diabetic nephropathy and diabetic retinopathy[227]. Whether RBP4 is elevated in obesity is controversial, as Yang *et al*[22/] found higher serum RBP4 Levels in obese individuals than in lean individuals. However, similar alterations were not found in the study by Korek *et al*[229] What is certain is that there is a correlation between elevated blood RBP4 Levels and the incidence of IR, serum lipid levels, and anthropometric parameters[224]. Wang *et al*[230] reported a significant decrease in RBP4 after LSG and concluded that

RBP4 Levels positively correlated with BMI, glucose, fasting C-peptide, and HOMA-IR. In another study, the authors found that RBP4 decreased after LSG in children and adolescents[231]. However, some studies have also shown that LSG did not significantly affect RBP4 Levels[232],[233]. In addition, Jüllig *et al*[234] found that RBP4 decreased more in patients after RYGB than after LSG. Fewer studies have been conducted on the effect of LSG on RBP4, and only sporadic studies have been reported; therefore, it is impossible to determine the changes involved. However, it is worth affirming that RBP4, as a specific adipokine, plays an important role in T2DM, and targeting RBP4 may become a potential therapeutic strategy.

4. GM, BAS, AND THEIR INTERACTIONS

4.1 GM

The human gut contains a unique variety of microbes, commonly known as the GM, which comprises approximately 3 million non-redundant microbial genes[235]. The GM may impact host metabolic functions, such as energy generation, steroid hormone synthesis, and bile salt metabolism, and they are intricately related to the development of metabolic diseases[236]. By increasing energy absorption from food, alterations in the GM, in particular, plays a significant role in the onset and progression of obesity and T2DM[237]. In obese people, the GM exhibits particular traits, including altered microbial gene abundance and ecological dysregulation which is linked to inflammation, increased body weight and fat mass, and T2DM[238]. Therefore, modifying the GM may be an option for treating T2DM and obesity. Studies have demonstrated that oral administration of improved GM to rats with metabolic syndrome increased insulin sensitivity[239]. Whether SG causes specific changes in the GM that contribute to improving metabolic disorders remains unclear. Tabasi *et al*[240] observed changes in the diversity and composition of the GM three months after LSG, and long-term follow-up studies showed that most changes remained for one year after surgery, indicating that SG elicits rapid and sustainable changes[241]. The alterations in GM due to RYGB and SG were varied, with RYGB increasing the relative abundances of the phyla Firmicutes and

Actinobacteria but reducing those of Bacteroidetes, whereas SG increased Bacteroidetes abundances. Of note, Roseburia species abundance was increased in all patients who achieved T2DM remission, which was common to SG and RYGB[241]. Changes in GM after LSG occur universally, which has been validated in several studies[242],[243]. This contributes to the various concerns regarding the degree to which the GM may impact the outcome of LSG and whether specific changes in the particular flora play a dominant role in improving T2DM or obesity. Surgery based on changed GM or fecal transplantation therapy may open new avenues for treating T2DM and obesity.

4.2 BAs

BAs are planar amphiphilic molecules with a carboxyl tail that are generated in the liver[244]. Diet regulates the synthesis, secretion, and circulation of BAs. In addition to the typical role of lipid absorption, BAs operate as signaling chemicals through two key receptors, i.e., Farnesoid X receptor (FXR) and Tekeda-G-protein receptor 5 (TGR5)[245]. The hepatic-intestinal cycle occurs when BAs are released into the duodenum after eating, and most of them are reabsorbed and transported back to the liver after they reach the ileum[246]. Current studies showed that BAs play a significant function in controlling lipid, glucose, and energy metabolism and that obesity and T2DM are associated with dysregulated BAs homeostasis in vivo[247]. Most respective studies confirmed that BAs alterations are similar in obese, T2DM, and IR patients, who show higher fasting BA levels than healthy controls[248]. However, this variation is not uniform, and many studies concluded that BA levels are not significantly altered[249]. The effect of LSG on BA levels is also somewhat controversial. Yang *et al*[133] revealed that BA levels exhibited a transitory decrease following LSG and thereafter a progressive increase. In contrast, following RYGB, BA levels show a consistently increasing trend. While Eiken *et al*[250] discovered higher BA concentrations after RYGB, increased inflow of BAs into the small intestine and more rapid release, this did not occur after LSG. Catoi *et al*[251] examined the relationship between IR and BAs after LSG and found no significant changes in BA levels and

HOMA-IR in the very early period (1 wk) after surgery. However, one month postoperatively, total BA levels increased, HOMA-IR decreased, and there was a negative correlation between them. In a different study, there was a link between higher BAs levels and better-glycated hemoglobin. Fasting and postprandial levels of total, secondary, and unconjugated BAs were higher after LSG[130]. Wang *et al*[252] discovered that after SG, total BA levels increased, and the fraction of 12-hydroxylated BAs was reduced in a diabetic rat model. This alteration may be fundamental to improved insulin sensitivity after SG. There are some differences between RYGB and LSG with regard to changes in total BAs after BS. One possible explanation for these differences is that RYBG entails changes in the structure of the gastrointestinal tract that affect the hepatic-intestinal circulation of BAs, whereas LSG does not. LSG and total blood BA levels and BA composition are unarguably linked; however, further research is required to help understand how certain BA species affect postoperative variations in LSG.

4.3 Interactions of BAs and GM

BAs and the GM interact in both directions (Figure 2). In the distal small intestine and colon, where most of the GM occurs, hydroxylation and dihydroxylation occur, through which the GM regulates the composition of BAs and controls the generation of secondary BAs[253]. By modifying the composition structure of BAs, the GM may further regulate FXR and TGR5 functions[254]. Biological agents that affect the GM can alter the BA profile[255], and BAs can affect the GM due to their antimicrobial effects and impact on intestinal mucosal integrity[256]. In conclusion, elucidating the relationship between BAs and the GM may provide a better understanding of the variability in weight reduction and enhanced glucose metabolism between RYGB and LSG. The stronger influence of RYGB on the GM owing to changed physiological channels induces alterations in BAs, whereas this effect is apparently minor after LSG.

CONCLUSION

LSG is an effective therapy option for the worrying pandemic of obesity and T2DM. LSG entails several therapeutic mechanisms that enhance glucose homeostasis and insulin resistance without relying on weight reduction. The gut-brain, gut-adipose tissue, gut-hepatic, gut-pancreatic, and gut-muscle axes are some of these putative entities. These insights may provide novel avenues for T2DM treatment targets focused on the gut. Overall, the understanding of how LSG works to treat T2DM has considerably advanced, however, further research is required. Additionally, while obese and T2DM patients may benefit from LSG, some hazards must be carefully considered, such as higher levels of certain GHs that may cause postprandial hyperinsulinemic hypoglycemia and decreased appetite, leading to malnutrition in non-overweight individuals.

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