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REVIEW

Role of Gut Microbiome and Microbial Metabolites in Alleviating Insulin Resistance After Bariatric Surgery

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Abstract

Insulin resistance (IR) is the most common pathophysiological change in patients with type 2 diabetes mellitus (T2DM). Several recent studies have suggested that the gut microbiome and microbial metabolites are involved in the pathogenesis of IR. Bariatric surgery, as an effective treatment for T2DM, can markedly alleviate IR through mechanisms that have not been elucidated. In this review, we summarize the current evidence on the changes in the gut microbiome and microbial metabolites (including lipopolysaccharide, short-chain fatty acids, branched-chain amino acids, aromatic amino acids, bile acids, methylamines, and indole derivatives) after bariatric surgery. Additionally, we discuss the mechanisms that correlate the changes in microbial metabolites with the postoperative alleviation of IR. Furthermore, we discuss the prospect of bariatric surgery as a treatment for T2DM.

Keywords Gut microbiota · Microbial metabolite · Bariatric surgery · Insulin resistance · T2DM

Abbreviations

IR	Insulin resistance
T2DM	Type 2 diabetes mellitus
GB	Gastric banding
RYGB	Roux-en-Y gastric bypass
SG	Sleeve gastrectomy
LPS	Lipopolysaccharide
SCFAs	Short-chain fatty acids
BCAAs	Branched-chain amino acids
AAAs	Aromatic amino acids
TMAO	Trimethylamine N-oxide
IPA	Indole propionic acid
BAs	Bile acids

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Introduction

Insulin resistance (IR), a major predisposing factor for type 2 diabetes mellitus (T2DM), is a clinical condition associated with decreased responsiveness to normal circulating levels of insulin [1, 2]. Observational studies have suggested that bariatric or metabolic surgery can rapidly improve the clinical and laboratory manifestations of patients with T2DM, including IR [3, 4]. There are various types of bariatric surgery, such as gastric banding (GB), Roux-en-Y gastric bypass (RYGB), and sleeve gastrectomy (SG) [4]. Bariatric surgery involves anatomically adjusting the digestion order of food through gastric volume reduction and removal of duodenum, which affects the composition and diversity of gut microbiota.

The human gut microbiota, whose total weight exceeds 1 kg, is a complex mutualistic system that comprises approximately 100 trillion bacteria [5–7]. The gut microbiota is essential for providing nourishment, regulating epithelial development, and modulating innate immunity and intestinal microenvironment [8]. The gut microbiota plays a key role in the development of IR and metabolic syndrome [2, 9]. Recent studies have demonstrated the correlation between IR and microbial metabolites, including lipopolysaccharide (LPS), short-chain fatty acids (SCFAs), amino acids (especially branched-chain amino acids (BCAAs) and aromatic amino acids (AAAs)), and bile acids [5, 10–13]. Studies on

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metabolomics will be vital to understanding the metabolic interactions between host and microbes and how microbial metabolites are associated with IR and T2DM.

In this review, we summarize the current evidence on the changes in the gut microbiome and microbial metabolites after bariatric surgery, with a focus on the impact of gut microbes and metabolites, on postoperative alleviation of IR. Additionally, we discuss the specific mechanisms that correlate the changes in microbial metabolites with the alleviation of IR after bariatric surgery, based on our current understanding of the functionality of microbial metabolism. Furthermore, we discuss the prospect of bariatric surgery as a treatment for T2DM. The potentiality of microbial metabolites is also mentioned, which work as indicators to evaluate the postoperative improvement of glucose homeostasis and as basis of other therapeutic approaches.

Alleviation of IR After Bariatric Surgery

Bariatric surgery, especially RYGB, is now recognized as the most effective treatment for T2DM and morbid obesity. In a randomized controlled trial of bariatric surgery and drug therapy, RYGB and SG exhibited a better therapeutic effect on T2DM than the traditional drug treatment [25]. Recently, a multicenter cohort study demonstrated that the RYGB group exhibited higher weight loss and alleviation of T2DM than the SG group [26]. The alleviation of IR symptoms is reported to occur very early after bariatric surgery and is independent of weight loss [27]. This suggests that the mechanism underlying the alleviation of IR and obesity is sequential or even causal. Previous studies have hypothesized that the exclusion of duodenum from the digestive tract after RYGB has the following two main effects: decreased hyperglycemia and increased glucose tolerance; modulation of the hormone level, which promotes the secretion of glucagon-like peptide-1 (GLP-1), peptide tyrosine tyrosine (PYY), and other substances to regulate satiety [28]. Meanwhile, increased GLP-1 secretion is reported to ameliorate insulin sensitivity of the islet β cells and stimulate insulin secretion [29], which subsequently alleviates the symptoms of IR and T2DM. However, the mechanism underlying the modulation of hormone levels after RYGB is still unclear. The gut microbiota and microbial metabolites may be potentially involved in the modulation of hormone levels after RYGB.

Changes in the Gut Microbiota Composition After Bariatric Surgery

A number of studies revealed that the gut microbiota of insulin-resistant patients or animal models comprises some unique components and structural characteristics. However, there is no consensus on these findings. At the phylum level, the insulin-resistant group exhibited a significantly higher abundance of Firmicutes than the control group. Additionally, the dominant flora in the control group was reversed in the insulin-resistant group. Thus, the ratio of Firmicutes/Bacteroidetes increased markedly in the insulin-resistant group [2, 30, 31]. At the genus level, the T2DM group exhibited significantly low levels of Akkermansia muciniphila, which belongs to the phylum Verrucomicrobia and is involved in mucin degradation. The transplantation of Akkermansia muciniphila into insulin-resistant recipient significantly improved insulin sensitivity and glucose tolerance and enhanced the Treg cell level [32]. However, most current studies have evaluated the microbiota in the animal models of T2DM with very few clinical trials. Additionally, IR is associated with significantly decreased levels of butyrate-producing bacteria, including Roseburia and Faecalibacterium prausnitzii, which markedly affect the production and secretion of metabolites that protect the intestinal barrier and promote insulin sensitivity [33, 34].

Bariatric surgery strongly promotes the remodeling of the gut microbiota. Previous studies have reported the postoperative enrichment of floral diversity. The increase in the proportion of butyrate-producing bacteria, such as Roseburia and Faecalibacterium prausnitzii, can improve insulin sensitivity of various tissues and organs [31, 35]. The abundance of γ-proteobacteria contributes to the postoperative improvement of the insulin signaling pathway [23]. The abundance of Bacteroidetes increases significantly after SG [36], which decreases the ratio of Firmicutes/Bacteroidetes. However, the change in the absolute value of Firmicutes and Bacteroidetes after bariatric surgery is still controversial [27]. Compared to the control group, the abundance of Firmicutes is significantly higher and that of Bacteroidetes is lower in rats after the duodenal-jejunal bypass (DJB) [37], and in clinical patients after RYGB [36]. Moreover, SG reshapes the diversity of the gut microbiota and improves the diurnal oscillation of the gut microbiota, which affects the host metabolism [38]. The findings of these studies indicate that the gut microbiota plays an important role in alleviating IR symptoms after bariatric surgery. However, the correlation between the phenotype of postoperative gut microbiota and the mechanism underlying the alleviation of IR has not been elucidated.

Changes in Gut Microbiota Metabolites After Bariatric Surgery

Several studies have elucidated some mechanisms underlying IR caused due to the disrupted composition and function of gut microbiota. However, the complete mechanism has not been elucidated. Various hypotheses, including chronic inflammation, intestinal barrier disturbance, and metabolic

disorders, have been proposed. In addition to several overlaps, there are few contradictions between these hypotheses. We highlight the preoperative and postoperative changes in microbial metabolites associated with IR in the following section (Table 1).

LPS

Lipopolysaccharides (LPS), a major component of the gram-negative bacillus (G-) cell membrane, play an important role in the immune response. Several studies have demonstrated that the LPS levels are high in the peripheral serum of T2DM model mice and patients with T2DM [7, 10, 39, 40]. The mismatch between the enhanced LPS level in the peripheral circulation and gut microbiota suggests severe impairment of the intestinal barrier. The expression of zonula occludens-1 (ZO-1) and occludin, which form tight junctions of the intestinal epithelium, is inhibited [41]. Thus, the bacteria colonized in the intestine and their metabolites enter the blood circulation from the intestinal cavity, which is called the translocation of LPS. LPS activates CD14/TLR4 to phosphorylate IRS through JNK and IKKβ, which leads to IR [42]. Additionally, the LPS-activated TLR4 induces the expression of inducible nitric oxide synthase (iNOS). The downstream S-nitrosation of the insulin receptor and IRS-1 impairs the insulin signaling and reduces insulin sensitivity in the liver, skeletal muscle, and adipose tissue [43–45].

The concentration of LPS and LPS-binding protein is markedly decreased in the peripheral serum after bariatric surgery. Meanwhile, the expression of inflammation-related receptors (CD14, TLR4, and TLR2), NF-κB DNA binding, and C-reactive protein (CRP) is significantly reduced after bariatric surgery [14, 46]. This indicated that LPS is involved in IR and that bariatric surgery plays an important role in the reduction of pro-inflammatory factors and endotoxins. Meanwhile, some studies have indicated the role of LPS-mediated inflammatory mechanisms in bariatric surgery to alleviate IR. Therefore, LPS may be used as an indicator to evaluate the postoperative improvement of glucose homeostasis and prognosis.

SCFA

Short-chain fatty acids (SCFAs) are the primary end-products of fermentation of non-digestible carbohydrates. SCFAs are generated by the gut microbiota inhabiting the cecum and colon. The main types of SCFAs are acetate, propionate, and butyrate [47–49]. Acetate is involved in energy production, lipid synthesis, and protein acetylation [50]. Propionate can serve as a substrate in the process of gluconeogenesis [51]. Butyrate is a major component of colonic epithelial cells [52], and plays an important role in maintaining intestinal barrier integrity and host metabolic homeostasis [13, 53]. Clinical investigations have revealed that the total amount of SCFA in the feces of the obese group is significantly higher than that of the lean group. The overweight and obese groups exhibited a high proportion of propionate [54]. One study demonstrated that the total SCFA concentration and the proportion of individual SCFAs in the feces of the patients remained unchanged or decreased during weight loss after bariatric surgery [15]. In contrast, another study using a mouse model reported that the RYGB group exhibited higher total amount of SCFA in feces, significantly lower levels of acetate, and significantly higher levels of propionate than the sham operation group [16]. It is unclear if the SCFA concentration in peripheral blood can reflect the changes in postoperative gut microbiota. The SCFA concentration in peripheral blood is affected by liver metabolism and endogenous fatty acids. A more accurate strategy is the determination of SCFA concentration in the portal blood, which is only applicable to patients undergoing complex abdominal surgery and those who have suddenly died [15]. The findings of the studies on the role of SCFA produced by intestinal flora in the occurrence of IR and the effect of bariatric surgery on its changes are unclear. Detailed studies are needed to elucidate these mechanisms.

SCFA is reported to exert a strong anti-inflammatory effect, which can alleviate the symptoms of IR by inhibiting the activation of NF-κB in the inflammatory signaling pathway [55]. Some studies have demonstrated that the oral administration of acetate can improve obesity and glucose tolerance in the T2DM animal models. The administration of acetate is reported to upregulate GLUT-4 gene expression [56, 57]. Moreover, targeted application of propionate in the human colon can significantly promote the secretion and release of PYY and GLP-1 [58]. Butyrate, which is metabolized by the gut microbiota, can reduce the relative abundance of IR-related bacteria, including Lachnospiraceae, Rikenellaceae, and Paraprevotellaceae, and alleviate IR symptoms by increasing the levels of p-AMPK and GLUT-4 in the adipose tissue [59]. Butyrate can also promote the generation and differentiation of Treg cells in the extrathymic tissue [60], which decreases inflammation and consequently alleviates the severity of IR. However, recent studies have demonstrated that increased acetate production resulting from the nutrient-gut microbiota interaction can cause increased glucose-stimulated insulin secretion and ghrelin secretion, as well as increased hyperphagia and obesity, through the microbiome-brain-β cell axis [61]. Additionally, further studies reported that acetate can be used as a substrate by the gut microbiota to produce butyrate, which plays an important role in modulating the microbiome composition, inhibiting adipogenesis, and alleviating IR [62]. Propionate was reported to increase the production of glucagon and fatty acid-binding protein 4 (FABP4), impair insulin activity, and promote IR in mice and humans [63]. This suggests that different types of SCFAs produced by the gut microbiota may play varied roles

Table 1 Changes in gut microbiota metabolites after bariatric surgery

Concentration of metabolit microbial	LPS	SCFAs	Acetate	Propionate	Butyrate	BCAAs	Leucine	Valine	Glutamate	AAAs	Tryptophan	KYN	Indole derivatives
Kind of surgery	RYGB	Biliointestinal bypass(-BIB)	RYGB	RYGB	RYGB		RYGB(GB has no significant effect)	RYGB(GB has no significant effect)	SG		SG	SG	
Lean patients	Low	Normal	NA			Normal	Normal	Normal	Normal	Normal	Normal	Normal	
Obese patients	High	High	NA	High	Low	NA	High	Increased by 28%	Increased by 29%	High	High	High	High	
After bariatric surgery	Reduced by from 0.567 U/-mL to 0.443 U/-mL after 6 months	Unchanged	Increased	Reduced from 75% to 62%	Increased from 12% to 27%	Unchanged	Reduced	Reduced by 18% after 3 weeks/ Reduced by 28% after 3 months	Reduced by 25% after 3 weeks/ Reduced by 33% after 3 months	Reduced considerably after 3 months		Reduced from 65 μM to 48.5 μM after 3 months / Reduced from 65 μM to 51.9 μM after 12 months	Reduced from 1.68 μM to 1.22 μM after 3 months / Reduced from 1.68 μM to 1.23 μM after 12 months	Increased after 3 months
Kind of research	Clinical research	Clinical research	Animal research	Animal research	Animal research	Clinical/Animal researches		Clinical research	Clinical research	Clinical research		Clinical research	Clinical research	
References	Monte et al. [14]	Sowah et al. [15]	Liou et al. [16]	Liou et al. [16]	Liou et al. [16]	Sowah et al. [15]/ Liou et al. [16]		Lips et al. [17]	Lips et al. [17]	Liu et al. [18]	Christensen et al. [19]	Christensen et al. [19]		Jennis et al. [20]

Concentration of metabolit microbial	IPA	Methylamines	TMAO	Bile acids	CA(primary bile acid)	GCA(primary conjugated bile acid)		TCA(primary conjugated bile acid)		DCA(secondary bile acid)	GUDCA (secondary conjugated bile acid)		GDCA (secondary conjugated bile acid)
Kind of surgery	RYGB		RYGB	RYGB	SG	SG	RYGB	SG	RYGB	SG	SG	RYGB	RYGB
Lean patients	High		Normal	NA	Normal								
Obese patients	Low		Unchanged	NA	Low	High	Low	NA	Low	High	Low	Low	Low
				Increased	Reduced								

Table 1 (continued)

After bariatric surgery	Increased from 4.4 μM to 10.5 μM after 12 months	Almost doubled		Reduced from 0.2 μmol/L to 0.09 μmol/L after 6 months	Increased significantly after 9.4 years	Reduced from 0.01 μmol/L to 0 after 6 months	Increased significantly after 9.4 years	Reduced from 0.24 μmol/L to 0.13 μmol/L after 6 months	Increased from 0.10 μmol/L to 0.26 μmol/L after 6 months	Increased significantly after 9.4 years	Increased significantly after 9.4 years
Kind of research	Animal research	Clinical research	Clinical research	Clinical research	Clinical research	Clinical research	Clinical research	Clinical research	Clinical research	Clinical research	Clinical research
References	Marius et al. [21]	Tremaroli et al. [22]	Andrew et al. [23]	Belgaumkar et al. [24]	Tremaroli et al. [22]	Belgaumkar et al. [24]	Tremaroli et al. [22]	Belgaumkar et al. [24]	Belgaumkar et al. [24]	Tremaroli et al. [22]	Tremaroli et al. [22]

in the pathophysiology of IR. Thus, there is a need to analyze specific SCFAs in further researches.

Furthermore, in addition to regulating biological functions, SCFAs function as carbohydrates. Excessive consumption of SCFAs increases the energy load of the body, which may affect its ability to alleviate IR. In addition to differences in the gut microbiota composition and microbial metabolites observed between the animal models and clinical patients and those caused due to various types of bariatric surgery, the diverse regulatory effects of different SCFAs may lead to different outcomes. SCFAs are critical mediators in the regulation of the gut microbiome. The regulatory mechanisms of specific SCFAs in alleviating IR after bariatric surgery must be carefully studied.

BCAA

Branched-chain amino acids (BCAAs) can be produced by the mammalian gut microbiota. BCAAs, such as leucine, isoleucine, and valine, are essential amino acids. However, high concentrations of BCAA are a major risk factor for IR and T2DM [11, 64]. The serum metabolomic analysis revealed that the insulin-resistant individuals exhibited a characteristic high serum BCAA concentration. The enhanced serum BCAA concentration was closely related to the enhanced BCAA biosynthesis by the gut microbiota and the downregulation of genes encoding bacterial inward transporters for BCAA [9]. Prevotella copri and Bacteroides vulgatus, which are abundant in the feces of patients with T2DM, contribute markedly to the metabolome changes in insulin-resistant patients. The abundance of P. copri and B. vulgatus is associated with increased levels of serum inflammatory factor IL-6 [65]. This indicates that the mechanism that triggers IR may be associated with metabolism-related chronic intestinal inflammation. In the animal models, the consumption of high-fat diet and P. copri resulted in various metabolic changes, including increased serum BCAA concentration, decreased glucose tolerance, and impaired insulin sensitivity, when compared to the control group [9]. This suggested that P. copri may increase the BCAA pool and contribute to the occurrence of IR. BCAA activates the mammalian target of rapamycin complex 1 (mTORC1), the key intersection of amino acids and insulin signaling pathway, phosphorylates IRS-1, negatively affects the insulin signaling pathway, and blocks signal transmission [66]. However, the specific reasons for the increase in BCAA concentration in the blood circulation of insulin-resistant patients are not clear. Additionally, the role of mTORC1 in the pathogenesis of IR is still unclear. The metabolome of insulin-resistant and obese patients is associated with elevated glutamate levels [67]. Recent studies have indicated that the elevated serum glutamate concentration in obese patients can be reversed by SG surgery, which is closely related to a glutamate-fermenting Bacteroides thetaiotaomicron [18].

This indicated that the alterations in the gut microbiota and microbial metabolites after metabolic surgery can alleviate the complications of obesity. However, the alleviation of IR as a mechanism for the alleviation of obesity has not been confirmed.

Clinical investigations have reported that obese patients exhibit a significant decrease in the BCAA levels after RYGB, which was independent of weight loss [17]. Further studies are needed to determine if the reduction in BCAA can be used as an indicator to quantify the postoperative effect of bariatric surgery. The postoperative reduction in the abundance of Clostridium decreases the bacterial protein hydrolysis, which subsequently reduces the production of BCAA in the intestinal lumen and the concentration of BCAA in peripheral blood [68]. However, most studies evaluating the postoperative variations in gut microbiota have only analyzed the microbiota at the phylum level [69]. There is a need for accurate identification of specific genera that affect BCAA production, such as P. copri and B. vulgatus. Therefore, the role of P. copri in decreasing the BCAA concentration after bariatric surgery must be evaluated in future studies.

AAA

The concentration of aromatic amino acids (AAAs), such as tyrosine, phenylalanine, and tryptophan (TPR), in the peripheral blood is closely related to the gut microbiota metabolism. The elevated levels of AAAs, which indicate the occurrence of IR, are an important risk factor for T2DM [11, 18]. Tryptophan is not absorbed in the upper digestive tract and can be metabolized by the intestinal flora to indole derivatives [70]. Indole derivatives are important microbiota-host signaling molecules and have a role in the pathophysiology of T2DM, which will be introduced in the next part. The peripheral concentrations of phenylalanine and tyrosine markedly decline after bariatric surgery [71, 72]. However, there is no direct evidence to correlate postoperative changes in these two AAAs and that of the gut microbiota. AAA and its derivatives derived from the intestinal flora metabolism are strongly correlated to the occurrence of IR. Kynurenine (KYN) is the main product of TPR degradation. KYN and its metabolites (including KYNA, QUIN, and NAD+) are actively involved in inflammation, immune response, and nerve excitability [73]. Some clinical studies have demonstrated that the peripheral serum concentration of KYN and its metabolites, as well as the ratio of KYN/TPR, are positively correlated with the occurrence of IR [74, 75]. One of the potential pathological mechanisms associated with the development of IR is the impairment of TRP-KYN metabolism, and there is clear evidence suggesting that the gut microbiota is involved in this pathological mechanism [73]. The levels of TRP, KYN, and its derivatives, and the ratio of KYN/TPR markedly decrease after bariatric surgery, which was positively correlated with weight loss and improvement of glucose homeostasis [19]. However, the correlation between the changes in the TPR-KYN metabolism after surgery and alterations in the gut microbiota remains unclear. The role of recently discovered intestinal flora metabolites with regulatory effects such as amino acids and their derivatives in alleviating IR after metabolic surgery must be evaluated in future studies.

Indole Derivatives

Indole, a signal molecule, is not endogenously produced by the human body. Indole is produced due to the enzymatic action of intestinal microbial tryptophanase. Indole functions as an interspecies signaling molecule in the immune, metabolic, and endocrine functions between the gut microbiota and the host. Indole and its derivatives are involved in the pathogenesis of metabolic syndrome [5, 76]. Indole propionic acid (IPA) is the indole derivative associated with IR. One clinical study reported that IPA is negatively correlated to the risk of developing T2DM [77]. The modification of gut microbiota after RYGB can reverse the low IPA levels in obese animal models [20]. The concentration of IPA in peripheral blood is reported to be positively correlated to the diversity of gut microbiota and some probiotics, including butyrate-producing bacteria (Faecalibacterium prausnitzii and Coprococcus), which were associated with postoperative alleviation of IR. The abundance of these bacteria increased after bariatric surgery. The IPA concentration was negatively correlated with acetate-producing bacteria, such as Blautia and Tenericutes, whose abundance decreased after bariatric surgery [78]. The mechanisms underlying the alleviation of IR by indole and its derivatives may be related to the protection of the intestinal barrier integrity and the recovery of chronic mild inflammation [79]. Meanwhile, indole may promote the secretion of GLP-1 through the regulation of L cells to alleviate IR symptoms [80]. However, it is difficult to identify the causal relationship between the decrease in blood glucose after bariatric surgery and the alleviation of IR induced by increased levels of indole and its derivatives because hyperglycemia can reduce the production of indole by inhibiting tryptophanase [81].

Methylamines

Trimethylamine (TMA) is a product of the intestinal microbiota-metabolizing precursors, such as choline and L-carnitine. TMA is mainly oxidized to trimethylamine N-oxide (TMAO) in the liver by flavin-containing monooxygenase 3 (FMO3), whose expression is regulated by bile acid-activated farnesoid X receptor (FXR) [82, 83]. A cohort study demonstrated a weak but significant correlation between the decreased TMAO levels and alleviation of IR [84]. One research has demonstrated that circulating TMAO

and its biosynthetic pathways may contribute to the regulation of glucose metabolism and insulin sensitivity [85]. The TMAO biosynthetic pathway involving FMO3 may be a novel target for the restoration of whole-body insulin sensitivity. The metabolism of TMAO is closely related to the gut microbiota. TMAO can be reduced to TMA by the gut microbiota (predominantly Enterobacteriaceae) [86]. The abundance of Enterobacteriaceae markedly increases after bariatric surgery [69], which indicated that the postoperative TMAO levels are reduced. Interestingly, in addition to alleviation of IR symptoms and chronic inflammation, the TMAO levels increase after bariatric surgery by approximately 2-fold when compared to those before surgery [21]. A similar increase in the levels of TMAO has been reported in patients after RYGB surgery [22]. The gut microbiota may utilize multiple pathways to regulate TMAO. The increased abundance of facultative anaerobic bacteria after surgery leads to a decline in the intestinal anaerobic metabolism [22]. The abundance of Pseudomonas containing TMA monooxygenase increases after bariatric surgery [87]. These mechanisms indicate that the levels of TMAO increase after RYGB. However, the genus that plays a major role in this process is unknown. Metabolic surgery is associated with increased TMAO levels and alleviation of IR at the same time. This indicated that metabolic surgery may block a pivotal node of the TMAO/FMO3 metabolic pathway, which is involved in IR signaling. Moreover, the elevated levels of TMAO following bariatric surgery may not significantly delay the process of IR alleviation. Further studies are needed to conclusively determine the role of elevated TMAO levels in alleviating IR.

Bile Acids

Bile acids are endogenous steroid molecules synthesized from cholesterol, which affects glucose and lipid homeostasis and energy expenditure. Bile acids can be reabsorbed in the ileum through the hepato-intestinal circulation. The gut microbiota plays a major role in the synthesis, metabolism, and reabsorption of bile acids in the body through the interaction between bile acids and their receptors [88, 89]. Primary bile acids, especially chenodeoxycholic acid (CDCA) [90], promote the release of FGF15/19 from the ileal epithelial cells by activating FXR (FGF15 in mice and FGF19 in humans), which inhibits gluconeogenesis and lipid production and improves glucose tolerance and insulin sensitivity [91]. FXR is also reported to be expressed in the enteroendocrine L cells. FXR exerts an inhibitory effect on GLP-1 secretion [92]. Additionally, CDCA can inhibit the secretion of pro-inflammatory adipokines (e.g., TNF-α and IL-6) through FXR, which promotes the secretion of insulin-sensitive adipokines (e.g., lipoprotein and leptin) to alleviate IR [93]. Secondary bile acids, especially lithocholic acid (LCA) and deoxycholic acid (DCA), function through Takeda G protein-coupled receptor 5 (TGR5). The activation of TGR5 promotes the enteroendocrine L cells to secrete GLP-1 [94], which then alleviates the symptoms of IR. The increase in GLP-1 concentration after RYGB surgery is strongly correlated to DCA, which acts on the receptor TGR5 and functions through downstream mTORC1 [95].

One clinical study demonstrated that the serum levels of primary bile acid decreased in patients 6 months after SG surgery, while those of the secondary bile acid increased significantly [24], which is closely related to the postoperative alterations of the gut microbiota. Moreover, an increase in the levels of glycodeoxycholic acid, a conjugated secondary bile acid, was significantly associated with an increase in insulin sensitivity after bariatric surgery [96]. Thus, the change in bile acid concentration depends on the specific type of bariatric surgery. Most studies indicate that circulating bile acids increase following RYGB and other malabsorptive procedures [23]. The increased circulating bile acid concentration following bariatric surgery can promote the secretion of FGF19 by activating FXR, which alleviates IR. This process is closely related to the abundance of Roseburia [27, 97]. However, the relationship between cause and effect remains unknown. Recent studies have suggested that bile diversion to the ileum (BG-IL) surgery can improve glucose homeostasis through the intestinal FXR-GLP-1 axis and alter intestinal bile acid availability. Additionally, the abundance of Akkermansia muciniphila increases after BG-IL independent of weight loss [98]. Bile acids contribute to the occurrence of IR by affecting the species of the intestinal flora and by being metabolized by the intestinal flora. The alterations in various bile acids and their derivatives after metabolism are still the current research hotspots.

Conclusions

The gut microbiota has been demonstrated to have a major influence on the alleviation of IR after bariatric surgery. However, no consensus has been reached on the underlying mechanism. In recent years, several studies have linked the gut microbiota to the postoperative alterations of the metabolome, which are crucial for the alleviation of IR. We comprehensively analyzed the changes in the gut microbiota and microbial metabolites after bariatric surgery and the role of these metabolites in the alleviation of IR. The analysis revealed that the gut microbiota and its related metabolites are involved in the pathogenesis of IR. Some microbiota can serve as a reference indicator to monitor or evaluate the alleviation of IR after metabolic surgery. Further studies on the regulation of IR by gut microbiota metabolites will provide a relevant theoretical basis for the selection of specific types of bariatric surgery or targeted drugs as an alternative to surgery for treating IR. The current studies are inadequate and further experimental

researches and clinical trials are needed to support and develop these conclusions, especially the crosstalk between gut microbiota changes, microbial metabolites, and IR symptoms after bariatric surgery.

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Compliance with Ethical Standards

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

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