Microbiota: a Sword that Breaks Through Diabetes

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Abstract: Diabetes are a group of metabolic disorders characterized by persistent hyperglycemia that is a major public health problem. Middle-aged and elderly people are at the highest risk of type 2 diabetes, but younger cases are now being diagnosed with greater frequency. Numerous clinical studies have reported that the behavior of the intestinal microbiota may affect the development of metabolic disorders in humans, including obesity and diabetes. This review describes the relationship between the gut microbiota and diabetes, and discusses the possible mechanisms underlying their involvement in the development of type 1 diabetes, obesity, and type 2 diabetes. By better understanding the intestinal microbiota, it may become possible to treat diabetes and obesity by manipulating the gut microbes through probiotics and dietary changes, fecal microbiota transplantation, or surgical approaches.

Key words: Microbiota; Type 1 diabetes; Type 2 diabetes; Obesity; Inflammation; Probiotics; Fecal microbial transplantation; Roux-En-Y gastric bypass; Sleeve gastrectomy

Introduction

Diabetes is a serious metabolic syndrome, and hyperglycemia is its main clinical symptom. The number of people with diabetes in China has risen sharply, which has brought a serious burden to China's economy and medical care system [1]. There are two types of diabetes. Type 1 diabetes is an autoimmune disease caused by the destruction of pancreatic β cells. Type 2 diabetes is a metabolic disorder that is often associated with obesity and overweight [2]. The human intestinal microbiota, also known as the "hidden organ", participates in the body's metabolism [3]. The intestinal microbiota plays a vital role in food absorption and the development of low-grade inflammation [4], which are two key processes involved in the development of obesity and diabetes. A large number of clinical studies have shown that the behavior of the intestinal microbiota may lead to metabolic disorders in the human body, including diabetes and obesity. This review describes the relationship between the gut microbiota and diabetes, and discusses the potential mechanisms by which the gut microbiota is involved in the development of type 1 diabetes, obesity, and type 2 diabetes. Obtaining a better understanding of the intestinal microbiota should aid in the treatment or prevention of these metabolic disorders.

Intestinal Microbiota and Type 1 Diabetes

Intestinal microbiota regulate the induction of type 1 diabetes under the influence of dietary factors, pH and gender

Type 1 diabetes is an autoimmune disease. Type 1 diabetes occurs when pancreatic β cells (which produce insulin) are destroyed by self-reactive T cells. Although type 1 diabetes is primarily caused by genetic defects, epigenetic and environmental factors play an important role in the development of the disease. Type 1 diabetes is related to human leukocyte antigen (HLA) II genes. Methylation of HLA genes can modulate gene expression [5]. Interestingly, Nielsen DS et al. [6] found that intestinal microbiota plays an important role in the development of type 1 diabetes in animal models. They showed that segmented filamentous bacteria (SFB) strongly affected the development of the immune system in non-obese diabetic (NOD) mice, which affected Th cell maturation and induced intestinal Th17 (IL-17 producing) cells [6]. SFB can promote IL-17-dependent immunity and autoimmune responses [7]. Wen L et al. [8] also demonstrated that NOD mice lacking the myeloid differentiation factor 88 (MyD88) protein, an adapter that recognizes microbial-stimulated innate immune receptors, did not develop type 1 diabetes. These studies suggest that changes in the gut microbiota are closely related to type 1 diabetes.

Changes in the intestinal environment can affect microbiota, thus affecting the occurrence of type 1 diabetes. The diet is a direct factor that influences both the microbiota and a variety of other risk factors (Figure 1). For example, a gluten-free (GLF) diet has been shown to have anti-diabetic effects in mice, possibly by altering the immune function and the composition of the gut microbiota, which is considered to be an immune-related environmental factor

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[9] (Figure 1). However, the relationship between gluten and diabetes is not well understood. Marietta EV et al. [10] studied NOD mice and found that differences in gut microbiota could be attributed to gluten-containing (GLC) and GLF diets. Another study suggested that gluten can affect the development of diabetes by changing the number of immune cells or by altering the cytokine/chemokine expression patterns [11]. Frisk G et al. also found that type 1 diabetes was related to the length of exposure to gluten [12]. In addition, studies have shown that the intestinal microbiota has both positive and negative roles on gluten-induced immunopathology in mice [13]. Thus, once the microbial balance is disordered, it will lead to the occurrence of type 1 diabetes.

In addition to dietary factors, the intragastric pH and gender are related to the microbial activity. Studies have shown that the pH of drinking water affects the composition of the intestinal microbiota and the incidence of type 1 diabetes [14]. Markle and colleagues found that female nonobese diabetic (NOD) mice had a higher incidence of diabetes than male NOD mice under specific pathogen-free

(SPF) conditions. Surprisingly, if the mice were fed a gluten-free diet, these differences disappeared [15]. This suggests that the gender difference in type 1 diabetes sensitivity depends on the activity of the microbiota. In support of this, another study recently found that the intestinal microbiota was the determinant of adolescent diabetes [16]. This brings hope to patients with type 1 diabetes, and may be useful for preventing the development of type 1 diabetes.

Inflammatory pathways by which microbiota induce type 1 diabetes

As noted above, the intestinal microbiota are important in the development of type 1 diabetes through the interaction of MyD88 with the host innate immune system (Figure 1). Under SPF conditions, the MyD88 signaling pathway is required for the development of autoimmune diabetes in NOD mice. Knocking down MyD88 in NOD mice can prevent the occurrence of type 1 diabetes. Toll-like receptors (TLRs) are innate pattern recognition receptors involved in host defense, which interact with MyD88 to control symbiotic bacteria and maintain tissue integrity [17].

Figure 1 Diagram of the pathogenesis of type 1 diabetes. At the genetic level, type 1 diabetes is related to HLA II genes. Gluten appears to be a dietary determinant of the disease. The GLF diet affects the development of type 1 diabetes by altering the composition and immune function of the gut microbiota. The presence or absence of gluten also appears to affect the onset of diabetes through cytokines/chemokines. In addition, gender and pH also affect the intestinal flora and are associated with the development of type 1 diabetes. SFB are involved in Th17 cell differentiation, thereby affecting the secretion of IL-17, which may induce type 1 diabetes. However, in the presence of other bacteria, SFB regulate the secretion of IL-17 by Th17 cells and inhibit the development of type 1 diabetes. TLRs recognize MyD88, which activates NF-κB and induces an inflammatory pathway. However, the gut microbiota also promote Treg to release IL-10 to reduce inflammation.

After the recognition of MyD88 by TLRs, NF-kappaB (NF- κ B) is activated to induce inflammation. The mechanism(s) underlying the regulation of immunity by intestinal microbiota remain to be elucidated. In a controlled study of 16 children with type 1 diabetes and 16 healthy children, the number of Actinobacteria and Firmicutes, and the ratio of Firmicutes to Bacteroidetes in the type 1 diabetes patients were significantly lower than in healthy children, and the number of Bacteroidetes increased significantly [18]. At the same time, when children developed autoimmune disorders, the number of Firmicutes was reduced and the number of Bacteroidetes was elevated [19]. Thus, changes in microbiota have a causative effect on type 1 diabetes. SFB are also involved in the autoimmune response of type 1 diabetes due to their effects on Th17 and IL-17. When the IL-17 levels are elevated in type 1 diabetes, there are potential pathogenic effects [20]. De Riva and colleagues compared two NOD mouse colonies, NODlow and NODhigh, and found that their cumulative incidences of type 1 diabetes were significantly different [21]. Therefore, SFB apparently inhibits the occurrence of type 1 diabetes through effects on Th17.

The inhibition of type 1 diabetes by SFB in NOD mice may also be related to the effects of other microbiota. Colonization of SFB in Germ-Free GF)-NOD mice did not protect the mice from type 1 diabetes. However, SFB could protect GF mice from type 1 diabetes induced by other symbiotic microbiota [7]. This phenomenon indicates that other bacteria in the intestine have a feedback-regulating effect on SFB-induced type 1 diabetes. Moreover, it was found that the lactic acid bacteria species present in the feces had a negative correlation with the occurrence of type 1 diabetes in a mouse model [22]. The intestinal microbiota also altered the development and function of lymphocytes, wherein the regulatory function of Foxp3⁺ T cells (Treg) was impaired [23]. However, single colonization of GF mice with bacteriocin can promote the differentiation of Treg and the production of the anti-inflammatory cytokine IL-10 [24].

Molecular mimicry also contributes to the pathogenesis of type 1 diabetes [25]. In view of the wide variety of intestinal microbiota, many bacteria have antigens similar to proteins of the pancreas [26]. For example, the Mgt protein of *Leptotrichia goodfellowii* and the islet-specific glucose-6-phosphatase-related protein (IGRP) have similar peptides. IGRP is a member of the G6Pase family and is specifically expressed in the pancreas [27]. The IGRP206-214 peptide is capable of activating diabetic NY8.3 T cells and inducing diabetes [28]. This phenomenon has also been observed with *Enterobacteria*. These findings suggest that certain bacteria are present in the gut and can induce or accelerate the development of type 1 diabetes through molecular mimicry. Therefore, the intestinal microbiota is considered to be an important environmental factor affecting the susceptibility to diabetes, and the underlying mechanisms

need to be explored.

Links Between Intestinal Microbiota, Obesity and Type 2 Diabetes

A high-fat diet leads to type 2 diabetes by inducing lipopolysaccharide-rich microbiota

In the past few decades, there has been an exponential growth of obesity and the associated metabolic syndrome and diabetes, leading researchers to pay increasing attention to the underlying mechanisms. Recent advances in next-generation sequencing technology and mechanistic experiments in gnotobiotic mice have confirmed that the intestinal microbiota is an environmental factor leading to obesity [29]. Several theories have been proposed to explain this relationship, and it has been suggested that the intestinal microbiota affect the energy balance, glucose metabolism, and low-grade inflammation, thereby inducing metabolic diseases such as obesity [30]. Compared with the intestinal microbiota of thin mice, Turnbaugh P et al. observed that the intestinal microbiota transplanted from obese mice was more likely to cause obesity in GF mice [31]. Interestingly, Backhed F et al. found that GF mice fed high-lipid foods gained less weight than conventional mice [32] (Figure 2). Studies have shown that a HFD can induce gut microbiota rich in lipopolysaccharides (LPS), thereby increasing the concentration of LPS in the plasma [33]. LPS is a microbial-associated factor that is continuously produced in the intestine as a result of lysing of Gram-negative bacteria [34]. Of note, Ley RE et al. found that the numbers of Firmicutes (typically Gram-positive) increased and Bacteroidetes (Gram-negative) decreased in obese mice [35]. Although this seems to be a paradox, this increased LPS is directly related to an increase in intestinal permeability, and is characteristic of metabolic endotoxemia. LPS interrupts the intestinal epithelium by inhibiting the expression of tight junction proteins, including zonula occludens-1 (ZO-1) and occluding [36]. Muccioli GG et al. found that the endocannabinoid (eCB) system [38] controlled intestinal permeability and lipogenesis. LPS controls adipose tissue metabolism by blocking cannabinoid-driven lipogenesis [38]. This has been postulated to be one of the causes of obesity. The translocation of LPS may be an early cause of insulin resistance [39]. In addition, LPS activates inflammasome proteins in macrophages. It also binds to and activates TLR4, and recruits downstream adapter molecule MyD88 to activate the NF- κ B pathway, which ultimately leads to inflammation [40]. In this process, MyD88 binds to the IL-receptor-associated kinase (IRAK1)-tumor necrosis factor receptor-associated factor 6 (TRAF6)-transforming growth factor- β -activated kinase 1 (TAK1) cascade [41], which mediates TLR4 signaling to NF- κ B. Eventually, it leads to the development of low-grade inflammation. TAK1 also interacts with c-Jun NH2-terminal kinase (JNK) [42]. A paper studied the subsequent signaling by JNK [43], and found that inhibition of the pathway could alleviate inflammation and insulin resistance. Among the

downstream proteins, insulin resistance is mainly induced by the serine phosphorylation of insulin receptor substrate-1 (IRS-1) by JNK [44]. Therefore, IRS-1 phosphorylation by serine is considered to be a marker of insulin resistance. The development of insulin resistance lays the foundation for the development of type 2 diabetes.

Intestinal microbiota regulates short-chain fatty acid metabolism, improving the resistance to obesity and type 2 diabetes

In addition to the role of LPS, short-chain fatty acids (SCFAs) are another factor related to the development of obesity. The most abundant types of SCFAs are acetate, propionate and butyrate (Figure 2). Acetate and propionate are mainly produced by Bacteroidetes, and butyrate is mainly produced by Firmicutes [45]. Acetate can improve glucose tolerance and butyrate can improve

insulin sensitivity and increase energy expenditure in mice, reducing the chance of obesity [46]. In addition, SCFAs regulate energy balance through a number of signaling pathways. SCFAs act as specific ligands for two G-protein coupled receptors (GPR), GPR41 and GPR43 [47], and thereby regulate intestinal epithelial cells. GPR41 is produced by enteroendocrine cells that regulate host energy balance through the gut microbiota. Activation of GPR41 stimulates the production of peptide YY (PYY) [48], which inhibits intestinal movement, and reduces energy extracted from the diet, affecting glucose utilization [49]. Thus, SCFAs enhance satiety and prevent obesity. Kimura et al. demonstrated that SCFAs-mediated GPR43 inhibits insulin signaling in adipocytes and promotes the metabolism of unbound lipids and glucose in other tissues [50]. In addition, SCFAs also activate glucagon-like peptide-1 (GLP-1) via GPR43, resulting in increased insulin sensitivity [51]. These

Figure 2 Diagram of the pathogenesis of type 2 diabetes and obesity. A HFD induces LPS-rich intestinal microbiota and increases the concentration of LPS in the plasma. LPS enhances intestinal epithelial cell permeability by destroying ZO-1 and occludin. LPS blocks eCB-mediated regulation of adipose tissue metabolism. The translocation of LPS activates inflammasome proteins in macrophages, inducing inflammation. At the same time, LPS binds to and activates TLR4 and recruits MyD88, activates IRAK-TRAF6-TAK1, and initiates signaling via the NF-κB pathway, which ultimately leads to inflammation. TAK1 also interacts with JNK, which induces inflammation and insulin resistance under the induction of IRS-1. In addition to LPS, SCFAs bind to GPR41 and GPR43. GPR41 induces PYY to enhance satiety and prevent obesity. The activation of GLP-1 by GPR43 results in an increase in insulin sensitivity. Microbiota inhibits FIAF and enhances LPL activity, reducing the development of obesity. The intestinal microbiota interacts with bile acids to bind FXR to TGR5 and activate GLP-1 to prevent diet-induced obesity, and thereby type 2 diabetes.

findings establish GPR43 as a sensor for excess dietary energy, which controls the utilization of body energy while maintaining metabolic balance. Some studies have also shown that GPR43 can enhance insulin sensitivity and inhibit inflammation [52], thus preventing the development of type 2 diabetes.

Intestinal microbiota inhibits fasting-induced adipocyte factor and participates in bile acid metabolism to reduce obesity and type 2 diabetes

One of the key mechanisms by which GF animals are not affected by diet-induced obesity is the presence of fasting-induced adipocyte factor (FIAF) [53]. FIAF is produced by intestinal epithelial cells and hepatocytes, and can inhibit the activity of lipoprotein lipase (LPL), leading to the accumulation of fat [54] (Figure 2). The intestinal microbiota can inhibit FIAF and enhance the activity of LPL [55]. In mice lacking the FIAF gene, LPL is more active, resulting in a 60% higher fat content compared to GF mice expressing the FIAF gene [56]. Therefore, FIAF participates in the regulation of intestinal microbiota-mediated fat storage. Alex et al. demonstrated that SCFAs induced FIAF by activating the nuclear receptor peroxisome proliferator activated receptor γ (PPAR γ) [57]. LPL is then further activated to inhibit the development of obesity.

Cholic acid and deoxycholic acid are the main bile acids synthesized from cholesterol in the human liver. Intestinal bacteria can convert primary bile acids into secondary bile acids [58] (Figure 2). In turn, the antibacterial activity of bile acids helps to inhibit the colonization and growth of microbiota in the gut. Studies have shown that the bacteriostatic action of bile acids mainly occurs through damage to the cell membrane [59]. In this process, primary bile acids activate the nuclear farnesoid X receptor (FXR), which binds to GPR TGR5. The TGR5 signal activates GLP-1 secretion and prevents diet-induced obesity [60]. Intestinal microbiota regulates human metabolism and influences obesity through LPS, SCFAs, FIAF and bile acids.

Researchers also found that a common feature of obesity and type 2 diabetes was the presence of low-grade inflammation in metabolic tissues [61]. Metabolic inflammation is characterized by the production of cytokines, including IL-6, IL-1, and tumor necrosis factor- α (TNF- α), all of which contribute to insulin resistance and diabetes [62]. Obesity may be the starting point of the low-grade inflammation. Studies have shown that gut microbiota may play an important role in type 2 diabetes by affecting body weight, SCFAs, pro-inflammatory activity, non-alcoholic fatty liver disease (NAFLD), insulin resistance, and by regulating gut hormones [63]. The induction of LPS by HFD can be demonstrated by injecting LPS into mice being fed a normal diet, which causes hepatic insulin resistance, glucose intolerance, and an increase in adipose tissue weight, which may eventually lead to type 2 diabetes

[64]. SCFAs have significant anti-inflammatory activity, and GPR43 activates GLP-1 to increase insulin sensitivity [65]. NAFLD is a family of liver diseases, including steatosis, fibrosis and cirrhosis, which are associated with obesity, insulin resistance, and diabetes [66]. In terms of fatty acid metabolism, bile acids activate the FXR-TGR5-GLP-1 pathway to prevent obesity [67]. This reduces the formation of type 2 diabetes to some extent. However, the role of microbiota in the pathways is not yet clear, and the underlying mechanisms need to be evaluated.

Treatment Strategy

Probiotics have been gaining increasing attention for the treatment of a variety of diseases [68]. When the host is given a sufficient number of probiotics, the probiotics have a beneficial effect on the host. However, the effects of different bacteria differ, and it is important to select the appropriate combination of bacteria to supplement [69]. A number of studies have shown that probiotic strains, particularly *Lactobacillus* and *Bifidobacteria*, have multiple beneficial effects on metabolic syndrome [70]. They can effectively reduce the incidence of both type 1 and type 2 diabetes, improving the quality of life for patients. They appear to promote weight loss and visceral fat reduction, improve glucose tolerance, and regulate intestinal inflammation [71] (Figure 3). *Lactobacillus* is involved in the metabolism and have demonstrated a number of beneficial effects, including reductions in the fat cell size and overall body fat [72]. Diet-induced obese mice showed a reversal of weight gain after being fed a particular *lactobacillus* [73]. *Lactobacillus* can reduce the intestinal mucosal permeability and improve the epithelial barrier function. They slow the progression of type 1 diabetes by inhibiting pro-inflammatory cytokines and inflammatory cytokines, and increasing IL-10 production. At the same time, these bacteria have also been shown to reduce LPS-induced vasomotor dysfunction to reduce inflammatory conditions and islet cell dysfunction [74].

Studies have shown that the beneficial effects of probiotic intervention on glucose tolerance and insulin sensitivity are associated with elevated levels of GLP-1 [75]. *Lactobacillus* can stimulate the production of GLP-1 and serve as a carrier for GLP-1, thereby exerting significant insulinotropic effects *in vivo* [76]. Due to all of these beneficial effects, *Lactobacillus* eventually possess anti-diabetic effects. An et al. found that *bifidobacteria* isolated from healthy Korean obese rats had anti-obesity and lipid-lowering effects in rats with obesity induced by a high-fat diet [77]. The *bifidobacteria* promoted the production of GLP-1 and peptide YY and led to the reduction of ghrelin [78] by regulating food intake. Further, *Bifidobacterium* can prevent diabetes by inhibiting bacterial blood transfer and adhesion to adipose tissue [79]. The oral administration of *bifidobacteria* increased the expression of insulin receptor β (IR β), IRS1, protein kinase B (PKB), I κ B kinase α (IKK α)

and nuclear factor-kappa B inhibitor α (I κ B α) protein, and decreased the blood glucose levels significantly [80].

Extracellular-signal regulated kinase (ERK) is a protease involved in the regulation of cell proliferation and differentiation. Alteration of the insulin receptor subtype activates the ERK pathway and is associated with abnormal proliferation and differentiation of intestinal epithelial cells in diabetic mice [81]. Probiotics such as bifidobacteria are involved in regulating the ERK pathway, increasing insulin sensitivity and resisting the onset of diabetes. In addition, in some studies, the effects of probiotics on diabetes were associated with increased levels of SCFAs, particularly butyrate in the colon. SCFAs may be a key component in the growth of lactobacilli and bifidobacteria and in reducing the intestinal pH, all of which are expected to have beneficial effects on diabetes [82]. Probiotics also reduce the storage of fatty acids and facilitate weight loss [83]. In addition, probiotics reduce inflammation by improving the intestinal barrier integrity and reducing the release of pro-inflammatory cytokines, thereby increasing the glucose alcohol content and insulin sensitivity [84]. This can reduce

the incidence of diabetes.

Recently, research on fecal microbiota transplantation (FMT) has attracted great interest. FMT has proven to be a successful method of treating recurrent *Clostridium difficile* infection (CDI) [85]. The FMT controls human gastrointestinal microbiota by transferring healthy donor microbiota into an existing disrupted microbial ecosystem. The effects are superior to those of antibiotics [86]. Although FMT has been in use for more than 50 years, it has recently gained new momentum. Turnbaugh PJ and colleagues completed a more in-depth study that transplanted the fecal microbiota from obese C57Bl/6J donors into GF-C57Bl/6J receptors. The GF mice showed a significant increase in their total body fat compared with the GF mice transplanted with the microbiota of lean mice [87]. In 2012, Vrieze A et al. studied the effects of FMT on insulin sensitivity in patients with metabolic syndrome. Patients with metabolic syndrome were randomly assigned to receive allogeneic or autologous microbiota. A significant increase in insulin sensitivity was observed in patients who were given microbial groups from lean donors [88]. Therefore, gut

Figure 3 Probiotics play an active role in anti-diabetes strategies. Lactobacillus improves the epithelial barrier function by reducing the intestinal mucosal permeability. Lactobacillus can inhibit pro-inflammatory or inflammatory factors to reduce the development of type 1 diabetes. Lactobacillus prevents the destruction of islet β cells by inhibiting Th1 via IL-10. Lactobacillus can reduce LPS-induced vasomotor dysfunction, thereby reducing inflammation status and islet cell dysfunction. Lactobacillus also stimulates the production of GLP-1 and achieves significant insulinotropic effects in vivo. Bifidobacteria promote the production of GLP-1 and PYY and the reduction of ghrelin, inhibiting fat formation. Bifidobacteria inhibit the production of type 2 diabetes by preventing the adhesion and transfer of microbiota. Patients can also increase the expression of IR β , IRS1, PKB, IKK α , and I κ B α by oral administration of bifidobacteria for therapeutic purposes. Bifidobacteria also participate in the regulation of the ERK pathway, increasing insulin sensitivity and resisting the onset of diabetes. SCFAs are also a key component in the growth of lactobacillus and bifidobacteria and in reducing the intestinal pH, which are all effects expected to be beneficial for diabetes.

microbiota can act as a synergist to increase the body's sensitivity to insulin, improving obesity and diabetes [89] (Figure 4). These findings have led to an interest in FMT for the treatment of other metabolic syndromes [90]. Although the causal relationship between gut microbiota and various diseases still needs to be confirmed, FMT may prove to be a powerful tool to provide diagnostic and therapeutic clues. In general, differences in the microbiota at the level of major phyla are not specifically related to disease. Studies of the intestinal microbiota should focus on deeper levels of classification or changes in intestinal microbial metabolites [91]. This should be a major direction for future research on FMT.

Impact of abdominal surgery on the microbiota

In addition to FMT, Roux-en-Y gastric bypass (RYGB) has also received much attention for the management of obesity and diabetes. RYGB results in a significant reduction of approximately 65%~75% of excess body weight and fat mass. This method not only causes a reduction in caloric intake or absorption, but also causes significant changes to the intestinal microbiota [92]. Chen H et al. first demonstrated that there is a link between changes in gut microbiota and changes in the monocyte phenotype and function after RYGB [93]. This may have

an important effect on chronic low-grade inflammation in type 2 diabetes patients. Further, Palreja A et al. found that 3 months after morbidly obese people underwent RYGB, the intestinal microbiota diversity increased, the oxygen tolerance increased, and the potential for nutrient utilization increased [94] (Figure 4). Sleeve gastrectomy (SG), which was developed before RYGB, also has a strong effect on type 2 diabetes and obesity, as well as the microbiota. Murphy et al. found that SG caused an increase in bacteroides while RYGB caused a decrease in the number of Firmicutes and Actinomycetes. However, through a KEGG localization and pathway analysis, the metabolic changes in intestinal microbiota after RYGB treatment were found to be significantly greater than those of intestinal microbiota after SG [95]. Duboc H et al. compared changes in intestinal microbiotic metabolites after RYGB and SG, and found that the postoperative bile acid production was highly protected by microbiota [96]. In addition, an experiment on the relationship between insulin sensitivity and the bile acids concentration after RYGB revealed that the presence of increased bile acids after metabolic surgery significantly improved insulin sensitivity [97]. These lines of evidence suggest that the intestinal microbiota has some ability to recover and can increase the sensitivity of insulin through alterations in bile acids and the subsequent weight

Figure 4 Guidance for the potential use of microbe-related techniques for the clinical treatment of diabetes and obesity. Probiotics treat diabetes by improving resistance to inflammation, increasing insulin sensitivity, and improving the function of islet cells. FMT fights diabetes by resisting obesity and increasing insulin sensitivity. After RYGB, the abundance of microbiota increases. As a result, nutrient utilization increases, oxygen resistance increases, and cardiovascular risk decreases. After SG, the abundance of microbiota is also improved, and the resistance to obesity is enhanced.

control. At the same time, due to changes in intestinal flow, the reduction of thick-walled bacteria and the increase of *Bacteroides* are beneficial to the synthesis of vitamin B12 and further increase the weight loss [98]. However, the specific mechanism is still not very clear. Overall, RYGB has more predictable and beneficial changes on the gut microbiota function than SG. In addition, a meta-analysis showed that RYGB was equally as effective as SG in treating diabetes in obese patients, but was associated with a significant reduction in cardiovascular risk [99]. Figure 4 demonstrates the clinical roles of the above techniques. With the help of these microbe-related technologies, the rates of diabetes and obesity will be greatly improved.

Outlook

In recent years, it has become clear that the intestinal microbiota is important in diabetes and obesity. Disturbances in the intestinal microbiota can damage pancreatic β cells and can also lead to obesity and diabetes. It has been found from experimental studies and clinical trials that probiotics may be effective in preventing and managing diabetes and obesity. In addition, diabetes and obesity can be effectively treated by interventions such as FMT, RYGB and SG. The results discussed in this paper are intended to illuminate the pathogenic roles of the gut microbiota in type 1 diabetes, type 2 diabetes, and obesity, and also to guide microbe-related pathways to improve diabetes and obesity. We hope that new insights into these pathways will be beneficial to the prevention and treatment of diabetes

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Conflict of interest

The authors declare that there is no Conflict of interest.

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