Mini-Review

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Prevention and treatment strategies for type 2 diabetes based on regulating intestinal flora

Dandan Xie[§], Xiaotong Zhao[§], Mingwei Chen[*]

Department of Endocrinology, the First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, China.

SUMMARY Diabetes along with related comorbidities associated with high disability rates severely threatens human health. The etiology of diabetes is complex. Genetics, environmental factors, eating habits, drug usage, aging, and lack of movement play important roles in the development of diabetes. Intestinal flora is reportedly closely related to the occurrence and development of type 2 diabetes. Herein, we review changes in abundance and proportion of intestinal flora in patients with type 2 diabetes and regulation of intestinal flora through diet, drugs, and surgery to prevent and treat type 2 diabetes. A more appropriate clinical diagnosis and treatment plan could be made considering changes in intestinal flora in the future.

Keywords type 2 diabetes mellitus, intestinal microbiota, insulin resistance, research progress

1. Introduction

With the development of the economy and society, the global urbanization process has accelerated, and people's lifestyle and dietary habits have changed dramatically. Excessive salt, sugar, and fat in the diet increase the incidence of chronic metabolic diseases, such as obesity and diabetes. According to the latest data released by the International Diabetes Federation, there were approximately 463 million people aged 20-79 years with diabetes worldwide in 2019. China has the highest number of adults with diabetes (116.4 million), accounting for a quarter of the world's diabetes-affected population. According to forecasting models, diabetes will affect 700.2 million people by 2045 (*1*). Type 2 diabetes mellitus (T2DM) accounts for more than 90% of the total number of diabetic patients. Hence, it is of great significance to study the pathophysiological mechanisms and effective prevention and treatment of T2DM.

T2DM is a metabolic syndrome caused by the combined effects of genetic and environmental factors, and is characterized by an absolute or relative deficiency of insulin secretion and a decrease in insulin sensitivity in target organs. Glucose metabolism disorder is the primary manifestation of T2DM, followed by metabolic disorders of fat, protein, water, and electrolytes. Insulin resistance and dysfunction of islet β cells are considered to be the leading causes of the occurrence and development of T2DM (*2*). The intestinal flora is known as "the second human genome". As an internal environmental factor of the body, it plays a vital role in regulating metabolism, immunity, inflammation, and other physiological and pathological processes. There is increasing evidence that abnormal intestinal flora is closely associated with the occurrence and development of T2DM (*3*).

More than 1,000 species of bacteria inhabit the human gut, and the total number is approximately 10^{14}, which is 10-fold more than the number of human cells. These microbes weigh up to 1.2 kg in total and account for about 80% of microbes in the human body. Bacteroidetes and Firmicutes are the two main phyla, followed by Actinomycetes, Proteobacteria, and Verrucomicrobia (*4*). Depending on their relationship with the host, intestinal flora can be divided into commensal bacteria, opportunistic pathogens, and harmful bacteria. In the physiological state, these organisms are mutually dependent and restricted. They have a symbiotic relationship with the human body and maintain a dynamic balance. Furthermore, commensals are a component of the natural defense line to maintain human health. When pathological factors break this balance, many diseases occur. Herein, we review the characteristics of intestinal flora in patients with T2DM and strategies for preventing and treating T2DM by regulating intestinal flora to provide a relevant reference for clinical diagnosis and treatment of diabetes.

2. Differences in intestinal flora between T2DM and non-diabetic populations

Although it is still uncertain whether there is a causal

Table 1. Differences in the intestinal flora among patients with T2DM, prediabetic population, and normal population in some studies

Study	Intestinal flora	Patients with T2DM	Prediabetic population
Zhang *et al*. (*5*)	*Akkermansia muciniphila* and *Faecalibacterium prausnitzii*	–	↓
	Bacteroides	↓	–
	Verrucomicrobia	↓	↓
Egshatyan *et al*. (*6*)	*Blautia and Serratia*	↑↑	↑
Larsen *et al*. (*7*)	Firmicutes	↓	–
	Proteobacteria and Bacteroidetes	↑	–
Wu *et al*. (*8*)	*Bifidobacterium* and *Bacteroides vulgatus*	↓	–
Sedighi *et al*. (*10*)	*Lactobacillus*	↑	–
	Bifidobacterium	↓	–
Hartstra *et al*. (*13,14*)	*Roseburia*, *Eubacterium hallii*, and *Faecalibacterium prausnitzii*	↓	–
	Lactobacillus gasseri, *Streptococcus mutans*, and *Escherichia coli*	↑	–

↑:The abundance of the intestinal flora increased in patients with T2DM/prediabetic population. ↓:The abundance of the intestinal flora decreased in patients with T2DM/prediabetic population. – :Not mentioned.

relationship between intestinal flora alteration and T2DM, the changes in the intestinal flora in patients with T2DM have been confirmed (Table 1). Zhang *et al*. found that the abundance of butyric acid-producing bacteria, such as *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* in the normal population was higher than that in the prediabetic population, and the abundance of Bacteroides in patients with T2DM was only half of that in the normal population and prediabetic population. The abundance of Verrucomicrobia in the prediabetic population and patients with T2DM was significantly lower than that in the normal population, and it may be a potential marker of T2DM (*5*). Egshatyan *et al*. reported that the abundance of *Blautia* and *Serratia* in the gut of the prediabetic population was lower than that in patients with T2DM, and people with normal glucose tolerance have the lowest abundance (*6*). Larsen *et al*. used real-time quantitative PCR to analyze the fecal flora in 18 patients with T2DM and 18 non-diabetic individuals and found that the abundance of Firmicutes decreased in patients with T2DM, whereas the abundance of Proteobacteria and Bacteroidetes increased. Besides, the ratio of Bacteroidetes to Firmicutes significantly positively correlated with blood glucose concentration (*7*). Wu *et al*. found that the abundance of *Bifidobacterium* and *Bacteroides vulgatus* in patients with T2DM was significantly lower than that in non-diabetic individuals (*8*). Karlsson *et al*. isolated the fecal microbiota from 53 patients with T2DM, 49 people with impaired glucose tolerance, and 43 healthy European women for metagenomic sequencing. They found that compared with the intestinal flora in non-diabetic individuals, 4 *Lactobacillus* species and 5 *Clostridium* species were increased and decreased, respectively, in diabetic patients. *Lactobacillus* positively correlated with blood glucose and glycosylated hemoglobin (HbA1c), whereas *Clostridium* negatively correlated with blood glucose, HbA1c, insulin, C-peptide, and triacylglycerol, and positively correlated with adiponectin and high-density lipoprotein (HDL) (*9*). Sedighi *et al*. analyzed the microbiome in fecal samples of patients with T2DM and normal populations. They confirmed that intestinal flora of patients with T2DM had a high abundance of *Lactobacillus*, whereas abundance of Bifidobacterium in healthy individual's intestinal flora was relatively high (*10*). Pedersen *et al*. analyzed the difference in serum metabiome and metagenome between 75 patients with T2DM and 291 healthy individuals. They found that when the proportion of *Prevotella copri* and *Bacteroides vulgatus* increased, the content of branched-chain amino acids (BCAAs) in serum increased, which induced insulin resistance and aggravated impaired glucose tolerance (*11*). Lambeth *et al*. studied the intestinal microbiota characteristics in patients with prediabetes or T2DM and healthy individuals. Compared to patients with T2DM, the abundance of Chloracido members in the prediabetic group was high, and an unknown genus of *Pseudonocardiaceae* was identified in the prediabetic group. The abundance of *Collinsella* and an unknown genera of family Enterobacteriaceae in patients with T2DM significantly increased compared with that of the other groups (*12*). Hartstra *et al*. reported that the abundance of *Roseburia*, *Eubacterium hallii*, and *Faecalibacterium prausnitzii* decreased in patients with T2DM, whereas that of *Lactobacillus gasseri*, *Streptococcus mutans*, and *Escherichia coli* increased (*13,14*). Reitmeier *et al*. analyzed the correlation between rhythmic changes in intestinal microbes and incidence of T2DM. The study involved fecal flora data from more than 4000 people in three German cohorts. It was found that both diversity of intestinal flora and relative abundance of specific flora fluctuated

at a periodicity of 24 h, and 13 operational taxonomic units (OTUs) that affect microbial rhythm disorders in T2DM were identified, which can accurately identify and predict T2DM (*15*). Sroka-Oleksiak *et al*. analyzed the duodenal flora and multiple clinical indicators of 17 obese individuals, 22 obese patients with T2DM, and 27 healthy individuals, and the results suggested that *Bifidobacterium* may be a biomarker for the occurrence and development of T2DM and obesity in the future (*16*). Gurung *et al*. summarized 42 studies on the relationship between intestinal flora and T2DM and concluded that *Bacteroides*, *Faecalibacterium*, *Akkermansia*, and *Roseburia* negatively correlated with T2DM, whereas *Ruminococcus*, *Fusobacterium*, and *Blautia* positively correlated with T2DM (*3*). Thus, the number and diversity of intestinal flora in patients with T2DM undergo different degrees of changes, and a regular analysis of the changes in intestinal flora has realistic directive significance.

3. Prevention and treatment of T2DM based on regulating intestinal flora (Figure 1)

3.1. Probiotics and prebiotics

Probiotics are a class of active microorganisms that have beneficial effects on host health. They affect host energy and substance metabolism by improving the host microbiota (*17*). At present, there are three main types of probiotics: strictly anaerobic *Bifidobacterium*, aerotolerant *Lactobacillus*, and facultative anaerobic cocci. Probiotic functions are mainly ascribed to six main aspects: promoting digestion and absorption, enhancing immune cells, protecting intestinal mucosa, curtailing cancer risk, reducing cholesterol absorption, assisting oxidation resistance, and loosening the bowel to relieve constipation (*18,19*). Prebiotics are food components that cannot be digested or difficult to digest, and these components are beneficial to the health of the host as they selectively stimulate the proliferation and/or activity of bacteria in the colon. Probiotics play a major role in defending against pathogens, regulating immune function, increasing absorption of minerals, improving intestinal function, regulating metabolism, regulating appetite, *etc*. (*20*). Several studies have reported that prebiotics (such as fructooligosaccharide an insulin-like fructan) and probiotics (such as *Saccharomyces boulardii*) can change the composition of intestinal flora, increase the relative abundance of *Bifidobacterium* and *Lactobacillus*, and improve glucose tolerance and lipid metabolism (*21-23*). A study showed that a daily intake of a 200 mL milkshake containing 4×10^8 CFU·100 mL^{-1} *Lactobacillus acidophilus*, 4×10^8 CFU·100 mL^{-1} *Bifidobacterium*, and 10 $g \cdot L^{-1}$ fructooligosaccharides can lead to a significant decrease in blood glucose level in patients with T2DM. In another study by the same team, prebiotic supplements for pregnant women with diabetes reduced blood sugar levels during pregnancy and 12 months after delivery, lowered insulin concentrations, and improved insulin sensitivity (*24,25*). Perraudeau *et al*. conducted a 12-week intervention in 76 patients with T2DM and found that probiotic supplementation with WBF-011 (containing inulin,

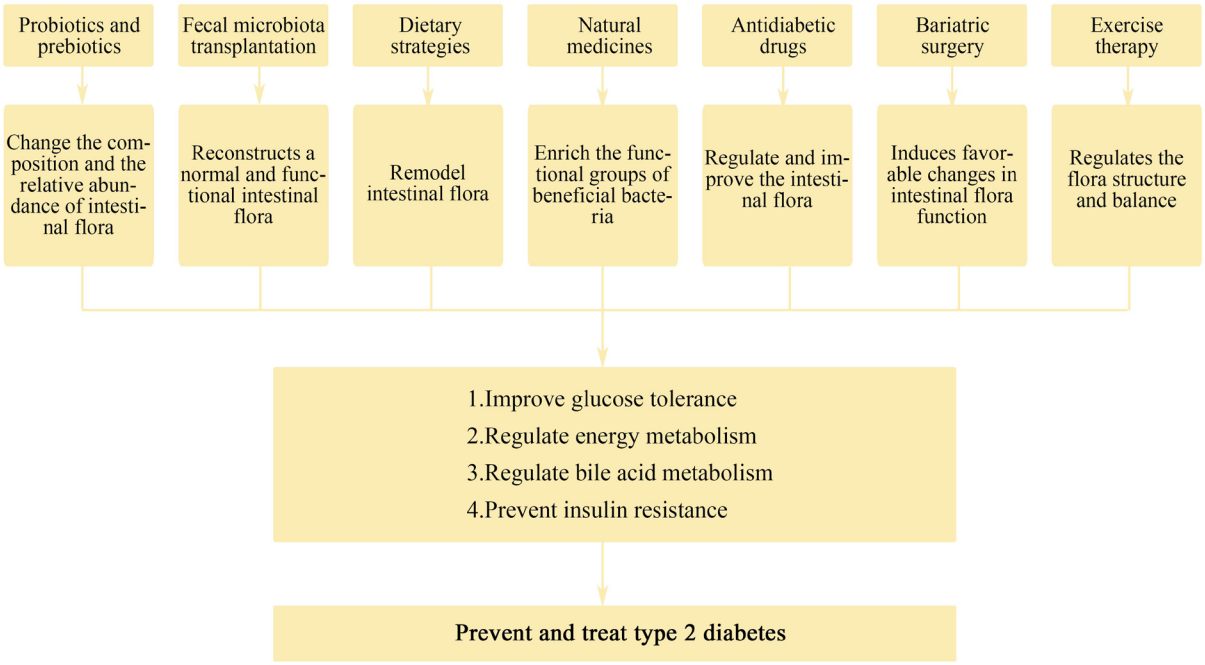

Figure 1. The possible mechanism of prevention and treatment of type 2 diabetes based on the effect of different strategies on the intestinal flora in various studies.

Akkermansia muciniphila, *Clostridium beijerinckii*, *Clostridium butyricum*, *Bifidobacterium infantis*, and *Anaerobutyricum hallii*) can significantly reduce postprandial blood glucose, HbA1c, and incremental glucose area under the curve with good safety and tolerability (*26*). Rittiphairoj *et al*. conducted a randomized controlled trial in approximately 2,000 patients with prediabetes or T2DM. The results showed that short-term or long-term probiotic use significantly reduced fasting blood glucose (FBG), HbA1c, and serum total cholesterol (TC). They also reported that probiotics more effectively reduced the HbA1c or FBG levels in patients not receiving insulin therapy (*27*). It is speculated that appropriate use of probiotics/probiotics can effectively prevent the occurrence and development of T2DM.

3.2. Fecal microbiota transplantation (FMT)

FMT has become a research hotspot in the medical field as a new treatment strategy. It is a technical system for treating intestinal diseases or extra-intestinal diseases by transplanting the functional flora from the feces of healthy people into the gastrointestinal tract of patients to reconstruct a normal and functional intestinal flora. FMT can be used to treat *Clostridium difficile* infection, irritable bowel syndrome, chronic constipation, inflammatory bowel disease, metabolic syndrome (hypertension, diabetes, fatty liver, obesity, *etc*.), autism, anxiety, depression, tumors, *etc*. (*28*). Vrieze *et al*. and Kootte *et al*. conducted controlled clinical trials to study whether the intestinal flora of thin people could improve blood glucose and lipid metabolism in men with metabolic syndrome. Six weeks after FMT, subjects who received FMT from thin people had significantly enhanced insulin sensitivity and increased abundance of intestinal flora compared with the control group. The results showed that the number of butyric acid-producing bacteria increased significantly. In addition, the subjects' plasma metabolites (such as γ-aminobutyric acid [GABA]) change, and butyric acid can regulate energy metabolism and prevent insulin resistance (*29,30*). Accordingly, FMT may be a good treatment option for patients with T2DM.

3.3. Dietary strategies

The major causes of T2DM are weight gain and abnormal visceral fat accumulation. They manifest as a large waistline and lead to metabolic syndrome and multiple complications. The control of obesity is more conducive to treat T2DM than drug intervention, and it can mitigate the progression of the disease at an early stage (*31*). Therefore, dietary therapy is key to the prevention and treatment of diabetes. Matacchione *et al*. reported that a diet rich in dietary polyphenols could effectively prevent T2DM by inhibiting the activity of α-amylase, α-glucosidase, and glucose transporters, stimulating insulin secretion, balancing hepatic glucose, preventing oxidative stress and inflammation-related hyperglycemia, and remodeling intestinal flora to improve blood glucose. The risk of developing T2DM is reduced by inhibiting or reducing intestinal transport of cholesterol and triglycerides, reducing serum cholesterol, triglyceride, and lipoprotein levels, and interacting with the synthesis and elimination of cholesterol and triglycerides to regulate lipid metabolism (*32*). Jiang *et al*. found that higher fruit intake is associated with a lower T2DM risk mediated by specific intestinal flora and metabolites. They found a correlation between fruit intake and the abundance of 31 OTUs belonging to *Faecalibacterium prausnitzii*, *Akkermansia muciniphila*, Ruminococcaceae members, *Clostridium*, *Acidaminococcus*, *Prevotella stercorea*, *Prevotella copri*, *Fusobacterium*, and *Enterobacteriaceae*. The fruit-flora index (FMI) was calculated based on the 31 OTUs associated with fruit intake. The FMI negatively correlated with the HbA1c level, and the risk of T2DM decreased by 17% for each additional unit of the FMI. Fecal metabolite sebacic acid positively associated with the FMI but negatively with T2DM risk. However, several other fecal metabolites negatively associated with the FMI were positively associated with T2DM risk. In a validation cohort of 6626 participants, T2DM risk was reduced by 10% for every additional unit of the FMI (*33*). Khursheed *et al*. reported that polysaccharides in mushrooms could play the role of prebiotics by regulating intestinal flora, metabolizing short-chain fatty acids (SCFAs) to increase the secretion of glucagon-like peptide (GLP)-1, and inhibiting gastric emptying to reduce appetite, thus playing an antidiabetic role (*34*). Therefore, cultivating good dietary habits (such as increasing the intake of fruits and vegetables) has an obvious effect on the prevention and treatment of T2DM.

3.4. Natural medicines

Xu *et al*. evaluated the clinical efficacy of different doses of *Gegen Qinlian* decoction in 187 patients with T2DM. The levels of FBG and HbA1c in patients treated with high and medium doses were significantly lower than those in the placebo and low-dose groups, and the therapeutic effect was dose-dependent. By analyzing the bacterial DNA in fecal samples of the subjects before and after treatment, they found a type of *Faecalibacterium prausnitzii*, which is closely related to the improvement of diabetes, was significantly enriched in the gut of patients after treatment. This increased bacterial load negatively correlated with levels of HbA1c and FBG, suggesting that alteration in intestinal bacteria is one of the crucial reasons for improvement in diabetes (*35*). Tong *et al*. randomly divided 450 patients with T2DM and hyperlipidemia into metformin and Chinese

herbal compound (AMC) treatment groups. After 12 weeks of treatment, 100 patients were randomly selected for evaluation of clinical efficacy. The results showed that AMC improved homeostasis model assessment of insulin resistance (HOMA-IR) and plasma triglycerides compared with metformin, and the increase in co-enriched bacteria represented by *Blautia* species was significantly associated with improvement in glycolipid homeostasis, which may improve hyperglycemia and hyperlipidemia by enriching functional groups of beneficial bacteria such as *Blautia* and *Faecalibacterium* (*36*). Tong *et al*. reported that Chinese herbal medicine and Chinese herbal prescriptions might improve glucose homeostasis and diabetes through the intestinal flora-mucosal immunity-inflammation-diabetes axis (*37*). Therefore, AMC may be beneficial to patients with T2DM, through its effect on the intestinal flora.

3.5. Antidiabetic drugs

In recent years, studies have found that some commonly used hypoglycemic drugs may regulate and improve intestinal flora in patients with T2DM to some extent, especially metformin (*38*). Metformin is recommended as a first-line oral drug to control blood glucose levels in patients with T2DM, and a meta-analysis showed that metformin increases abundance of bacteria that produce SCFAs in subjects with T2DM (*39*). Sun *et al*. treated patients newly diagnosed with T2DM with metformin and found that composition of intestinal flora changed significantly (Figure 2). *Bacteroides fragilis* decreased most significantly among other species; and levels of glycoursodeoxycholic acid (GUDCA) and tauroursodeoxycholic acid (TUDCA) in the gut increased. GUDCA and TUDCA are farnesoid X receptor (FXR) antagonists, and metformin increases the GUDCA level by reducing abundance of *Bacteroides fragilis* to inhibit activity of bile salt hydrolase. Metformin inhibits intestinal FXR signals independently of intestinal adenosine monophosphate-activated protein kinase, significantly increases the production of active GLP-1, and improves glucose homeostasis (*40*). According to the results of Forslund *et al*., metformin can improve the intestinal flora of patients with T2DM, promote the production of SCFAs such as butyric acid and propionic acid, stimulate intestinal gluconeogenesis, and increase insulin sensitivity in the body (*41*). In a clinical trial, 95 patients with T2DM were randomly divided into two groups: group A received acarbose 150 mg/d and group B received the same treatment as group A but without acarbose. The results showed that compared with group B, intestinal *Bifidobacterium* increased, and serum lipopolysaccharides and prothrombin activator inhibitor 1 significantly decreased in group A. Acarbose therapy can significantly increase intestinal *Bifidobacterium* in patients with T2DM and reduce the levels of some inflammatory factors besides

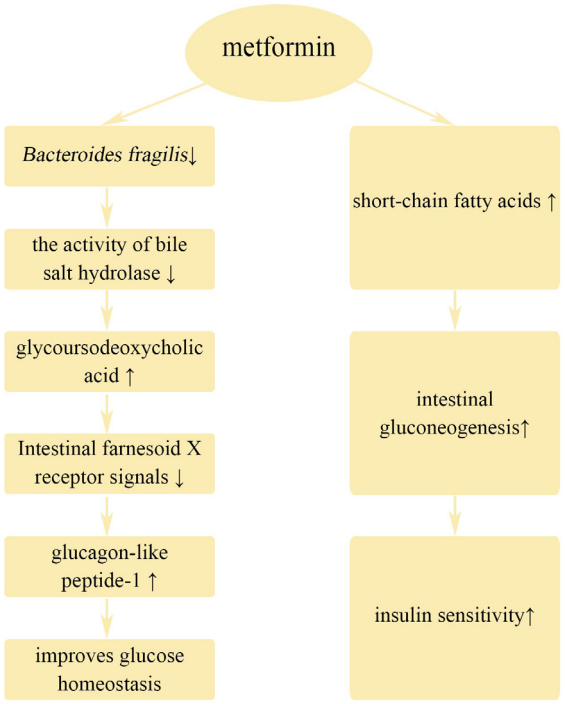

Figure 2. The mechanism of metformin in the treatment of diabetes by regulating intestinal flora. ↑:increase; ↓:decrease.

reducing blood glucose (*42*). Gu *et al*. randomly divided 106 patients with new-onset T2DM into two groups: those treated with acarbose 300 mg/d or glipizide 5-10 mg/d for 3 months. The results showed that acarbose was superior to glipizide in reducing glucose and lipid levels, body weight, and insulin resistance. Treatment with acarbose significantly increased the abundance of various probiotics (such as *Bifidobacterium* and *Lactobacillus*) and substantially reduced the abundance of *Clostridium* and *Bacteroides*, while there was no significant change in the glipizide group before and after treatment. Acarbose likely regulates glucose and lipid metabolism by changing the bile acid (BA) metabolism of intestinal microbes and affecting the host BA signal, thus achieving benefits other than the hypoglycemic effect (*43*). Accordingly, when choosing antidiabetic drugs, a more beneficial treatment plan for patients can be developed by taking into account the effects of drugs on intestinal flora.

3.6. Bariatric surgery

Linner and Kremen performed the world's first jejunoileal bypass surgery in 1954, pioneering the surgical treatment for obesity. A large number of randomized clinical trials comparing various surgical interventions with non-surgical interventions for diabetes have consistently demonstrated the former's advantage in improving all glucose variables and other metabolic aspects (*44*). At present, the widely accepted surgical procedures in metabolic and bariatric surgery include

laparoscopic sleeve gastrectomy (LSG), laparoscopic Roux-en-Y gastric bypass (LRYGB), and biliopancreatic diversion with duodenal switch. Among them, LSG and LRYGB are the most common types of bariatric surgery. For patients with T2DM, bariatric surgery plus medication is more effective than medical therapy alone. Magouliotis *et al*. found that after metabolic surgery, patients' blood glucose, insulin, triglyceride, TC, low-density lipoprotein, and HDL levels; HOMA-IR; food intake; and the rate of diabetes remission were significantly improved. Postoperatively, the levels of BCAA decreased, whereas those of trimethylamine-N-oxide (TMAO), GLP-1, GLP-2, and peptide YY (PYY) increased (*45*). LRYGB and LSG can reduce blood glucose level and body weight in obese patients with T2DM and increase *Roseburia* species. Compared with LSG, LRYGB can induce more favorable changes in intestinal flora function. LRYGB led to an increase in the abundance of Firmicutes and Actinobacteria phyla and a decrease in Bacteroidetes phyla, whereas LSG led to an increase in the abundance of Bacteroidetes phyla (*46*). Reports have suggested that bariatric surgery may change the microbiome; furthermore, it has been suggested that intestinal flora may play a role by increasing the absorption of energy in the diet and altering signaling pathways of metabolism and appetite. Clinical studies have shown that circulating BA concentration increases after bariatric surgery, and the total circulating BA concentration in LRYGB patients positively correlates with serum GLP-1 concentration and negatively correlates with postprandial blood glucose concentration. The increased concentration of circulating BA may be due to changes in the anatomical structure and intestinal microbiota caused by bariatric surgery (*47*). Bariatric surgery may be one of the most effective treatments for T2DM.

3.7. Exercise therapy

Exercise therapy in diabetes is mainly suitable for patients with mild and moderate T2DM, especially in obese individuals with T2DM. Exercise can increase the abundance of beneficial intestinal flora and regulate the flora structure and balance. It also significantly enhances the intestinal flora's ability to synthesize SCFAs, decompose BCAAs, and promote secretion of hormone PYY. Furthermore, it inhibits appetite and plays a key role in weight loss, improving insulin resistance, and regulating blood glucose. Low-grade inflammation is a characteristic of T2DM. Moderate running can prevent excessive activation of the immune system, and regular exercise such as endurance training in the form of stationary exercise bikes, aerobics, dumbbell, and other forms, and flexibility training, such as static stretching, can significantly improve the index of glycolipid metabolism and inflammation in patients with T2DM. In addition, the abundance of fungi, *Candida albicans*, and mycotoxins can be significantly reduced by exercise without affecting beneficial bacteria such as *Lactobacillus* and *Bifidobacterium* (*48*). Liu *et al*. randomly divided 39 overweight men with prediabetes into two groups: one group performed 12 weeks of intense exercise and the other group maintained a sedentary lifestyle. After 12 weeks of one-to-one exercise training, all participants had significant and comparable reductions in body weight and body fat percentage without any drug and dietary interventions, while the individual differences in fasting glucose, insulin, and HOMA-IR were significant. Further studies showed that the ability to synthesize SCFAs and GABA and decompose BCAAs was significantly enhanced in the intestinal flora of exercise responders. Whereas, the intestinal flora of non-responders synthesized a large number of products that were not conducive to glucose metabolism, such as BCAAs and aromatic amino acids. These results suggest that intestinal flora and its metabolites mediate improvement in insulin sensitivity and glucose homeostasis by exercise. They are expected to be biomarkers for evaluating and predicting the efficacy of exercise intervention in future studies. Thus, intestinal flora intervention may help maximize the health benefits of exercise (*49*).

4. Summary and outlook

A growing number of studies have shown that intestinal flora is closely related to occurrence and development of T2DM. Intestinal flora may be involved in T2DM pathogenesis *via* multiple metabolic pathways, such as those mediated by SCFAs, BA metabolism, endotoxin, and TMAO. Regulating intestinal flora by bariatric surgery, probiotics, FMT, exercise, establishing healthy eating habits, antidiabetic drugs and other methods can improve insulin resistance and regulate blood glucose. Although new therapeutic methods are being developed, many uncertainties and potential risks must be accounted for, warranting further investigation.

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[§]These authors contributed equally to this work.
**Address correspondence to:*
Mingwei Chen, Department of Endocrinology, The First Affiliated Hospital of Anhui Medical University, No. 218 Jixi Road, Hefei 230032, Anhui, China.
E-mail: chmw1@163.com

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