

# ***Probiotic Studies Advancements about the Therapy of Type 2 Diabetes Mellitus***

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**Abstract:** Type 2 diabetes Mellitus (T2DM), as the highest incidence of diabetes mellitus, has brought great troubles to many patients, seriously affecting their physical and mental health. Due to the characteristics of long-term management, existing treatment schemes are complicated to operate and difficult to maintain. New therapeutic means using probiotics to improve intestinal flora may become the key to break through this difficulty. This article briefly describes the symptoms of T2DM and the relationship between intestinal flora and probiotics, summarizes the evidence-based evidence on probiotics in the treatment of T2DM in recent years, and summarizes the related mechanisms and potential functions of probiotics in the therapy on T2DM. The agenda of this scrutiny is to supply a theoretical foundation to support the management of other chronic diseases, encourage the development of more efficient methods for the therapy of type 2 diabetes, and fully utilize the abilities of probiotics in this area.

**Keywords:** Type 2 diabetes mellitus, Intestinal flora, Probiotics

## **1. Introduction**

Type 2 diabetes Mellitus (T2DM) is for extended periods metabolic complaint which accounts for 90% of the onset of diabetes. Increased thirst, frequent urination, insufficient insulin secretion, hyperglycemia, coronary artery disease kidney disease, eye and foot disorders, coronary heart disease, and chronic cognitive impairment comprise a number of its indicators. As of 2021, the global prevalence of diabetes has exceeded 10%, with nearly 540 million people worldwide encounter with diabetes. Among them, the prevalence of diabetes among young, middle-aged and elderly people is nearly 11% (536.6 million people), and it is expected that by 2045, this figure will rise by 2.2 percentage points (783.2 million people) [1]. The prevalence is higher in middle-income nations among the various income levels. In China, 9.7 % of adults over the age of 20, or 92.4 million, have diabetes, or nearly 100 million people, according to the study. And nearly 16%, or 148 million, belong to the diabetes "reserve army"--pre-diabetes. By 2024, China will have nearly 150 million people with diabetes, more than 90% of whom have T2DM. This disease has a huge negative impact on global economic development [1]. With the in-depth study on T2DM, a variety of treatment schemes have been developed one after another. In recent years, the new treatment scheme for T2DM is to prevent, relieve and treat T2DM by improving intestinal flora.

Intestinal flora is a complex system in the gastrointestinal environment and the largest microecosystem in the human body, so it is considered to be a sheltered "organ". Intestinal flora helps the body to complete the transformation from metabolites to micronutrients through its powerful

metabolic action [2]. Among them, genetic and acquired factors (including multiple factors such as individual living habits, nutritional style and type) may affect the homeostasis of intestinal flora in the body, thus affecting gastrointestinal mucosal permeability and host immune system [2]. It can be affirmed that intestinal flora makes a crucial effect in maintaining the healthy homeostasis and is also an important factor affecting T2DM. In T2DM patients, the intestinal flora is significantly different from the healthy people. For example, the abundance of  $\beta$ -Proteobacteria is significantly higher. A couple of metabolites of this intestinal flora can enter the systemic circulation with the help of a variety of receptors, and act as signaling molecules to affect multiple physiological processes including cell function, oxidative stress and metabolism, which are closely related to blood glucose level. Thus, affecting the development of T2DM [3].

Probiotics, as a general term for a class of microorganisms beneficial to human health, can maintain the balance of gastrointestinal flora in the body when it reaches a certain amount, and provide benefits to human health by producing vitamins, participating in food digestion and inhibiting the proliferation of harmful microorganisms [4]. It can regulate intestinal flora, inhibit inflammatory response, improve intestinal barrier function, antagonize pathogens, balance intestinal pH value, stimulate immune system, and produce beneficial microbial metabolites, such as short-chain fatty acids (SCFAs) [5]. Probiotic intervention is a novel strategy with great potential in T2DM management [2]. Put another way, probiotics' capacity to prevent the growth of dangerous bacteria can control the process in intestinal flora and create a successful treatment plan for T2DM.

By summarizing the current research results of probiotics in the treatment of T2DM, this paper discusses the innovation and application value of probiotics in T2DM and provides basis and research ideas for subsequent in-depth study.

## 2. Application and Mechanism of Probiotics in T2DM

### 2.1. Application of Probiotics in T2DM

In an 8-week study, a single strain of probiotics was used to divide 40 T2DM patients into a probiotic group (taking a capsule containing  $10^8$ cfu *Lactobacillus casei* daily) and a placebo control group (taking capsules containing maltose). At the beginning and end of the study, the patients' physical condition, consumption statistics and blood samples were analyzed [6]. The results showed that fasting blood glucose (FPG, 164.2  $\rightarrow$  135.84), insulin Concentration (17.22  $\rightarrow$  14.89) and insulin resistance (IR, 123.14  $\rightarrow$  93.42) in the probiotic group were dramatically fewer than other in the placebo group [6]. These results indicated that *Lactobacillus casei* significantly improved the blood glucose and insulin levels, providing a clinical basis for demonstrating the active effect of probiotics on the treatment to T2DM patients.

Similarly, 74 T2DM patients were randomized to three groups at random throughout a 9-month stochastic, placebo-controlled research. energetic *Lactobacillus reuteri* ADR-1, heat-inactivated *Lactobacillus reuteri* ADR-3, and a placebo were administered to them [7]. After statistical analysis, it was found that after taking *Lactobacillus reuteri* capsules, the irreversible reaction of carbohydrate occurrence in serum was reduced, the carbohydrate degradation reaction continued to increase, and the FBG was decreased in patients. Following three months of monitoring, the improvement effect of probiotics on FBG still existed after discontinuation, indicating that the influence of *L. reuteri* on patients' homeostasis is sustainable and stable. Microbiota analysis revealed that the probiotic group had a expressively higher level about *Lactobacillus reuteri*, and that the change in FBG was positively connected with bacteroidetes or with the ratio of bacteroidetes to Firmicutes and negatively associated and the up-regulation of *Lactobacillus reuteri* [7]. The above results indicate that the two strains of *Lactobacillus reuteri* have significant effects in T2DM. Studies have found that *L. reuteri* may play a positive role in improving T2DM by regulating cytokine levels, increasing the activity of

corresponding enzymes and regulating the proportion of intestinal flora. In the future, bacterial levels in fecal excreta after ingestion of two types of *Lactobacillus reuteri* can be used to predict FBG and other indicators of T2DM patients, which can be used as an effective basis to infer whether T2DM can be alleviated and treated [7].

Another meta-analysis included 30 randomized controlled trials (n=1827), in which probiotics (*Lactobacillus* and *Bifidobacterium*) with colonies of 107 to 1012 were used for 1-9 months. The sequelae showed that, Probiotic recruitment drastically dwindle FBG (SMD=-0.331,  $P < 0.001$ ) and increased insulin levels (SMD=-0.185,  $P = 0.004$ ) and significantly decreased HbA1c levels (SMD=-0.421, 95%,  $P < 0.001$ ). It also significantly reduced HOMA-IR score in T2DM patients (SMD=-0.224, 95%,  $P < 0.001$ ) [8]. The above results directly indicate that probiotics supplementation has a significant positive effect on the treatment of T2DM, indicating the value of probiotics in the treatment of T2DM.

Breakthroughs have also been made in the management of T2DM with probiotics combined with other drugs. Metformin, a widely used drug in the treatment of diabetes, can play a significant therapeutic effect by inducing weight loss and enhancing glucose control. Some studies suggest that its primary effect is on the liver, improving symptoms in T2DM patients, such as high fasting blood glucose (FBG), elevated serum glycosylated hemoglobin (HbA1c) levels, and insulin resistance (IR) [9]. In the trial of patients treated with metformin combined and probiotics, a randomized controlled pilot study was conducted to include 60 adults with prediabetes or T2DM. Different strains of probiotic treatment groups and metformin and probiotics combined treatment groups were set up, and the diet and exercise status of the subjects were recorded daily through capsule administration. After 12 weeks of treatment, the analysis of the participants who received the combination of metformin and probiotics showed that probiotics could play a role as an adjuvant to metformin by building the manufacture of short-chain fatty acids, thereby enhancing the problem about intestinal mucosal dyspepsia and playing a hypoglycemic role in the intestine [9]. In a word, the combination of metformin and probiotics may improve FBG and IR, possibly by affecting the composition of intestinal microbiota in diabetic patients, thus playing a catalytic auxiliary role in treatment.

## 2.2. Mechanism of Probiotics Intervention in T2DM

### 2.2.1. Probiotics Treat Intestinal Inflammation and Oxidative Stress

Climbed intestinal permeability and minimal inflammation are common in T2DM patients. These conditions can usually be brought on by an imbalance in the intestinal flora, which increases intestinal permeability and induces bacterial endotoxins to enter the body, causing inflammation and ultimately hyperglycemia. Obesity is also a typical clinical symptom. Excessive adipose tissue continues to release a pro-inflammatory cytokine named tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) [10]. Studies have shown that TNF- $\alpha$  can activate protein kinase C (PKC) and phosphorylate amino acid residues on insulin receptor substrate, thus promoting insulin inactivation, which is an important cause of insulin resistance. Through the modulation of pro-inflammatory cytokines, including TNF- $\alpha$ , interleukin-6 (IL-6), and C-reactive protein, coupled with the enhancement to anti-inflammatory cytokines particularly interleukin-4 (IL-4), probiotic supplementation demonstrates significant therapeutic potential in improving intestinal barrier function and alleviating type 2 diabetes mellitus [10].

In an animal experiment, a mouse model with congenital obesity and T2DM and IR was treated with probiotic and fed *bifidobacterium lactobacillus* subspecies 420 for a period of 6 weeks. The results showed that *bifidobacterium* could weaken metabolic endotoxemia, inflammation and endotoxin translocation and enhance oxidative stress [11]. During the experiment of diabetic High-fat diet induced mice, when the mice initially became obese, the homeostasis of intestinal flora was broken, and more bacteria entered the adipose tissue, promoting the increase of mucosal adhesion.

When T2DM is fully developed, these live bacteria are colocalized in the same structure or region as dendritic cells in the gut. Moreover, studies have shown that this mechanism requires CD14, which is a leukocyte differentiation antigen that can recognize different receptors in bacteria, so as to maintain the body in a state that is not conducive to blood glucose recovery such as insulin resistance [11]. In addition, the lack of leptin, which mitigated these colocalization effects, led to severe obesity in mice. In order to solve the problem of bacteria entering adipose tissue, probiotics were used in the experiment to intervene in T2DM experimental mice, and it was found that endotoxin translocation and bacterial co-localization were positively affected, indicating that probiotics have unique advantages in regulating intestinal homeostasis to solve the oxidative stress caused by T2DM [11].

### 2.2.2. Probiotics can Improve Body Metabolism and Insulin Sensitivity

An increasing amount of research demonstrates that the SCFAs generated by probiotic fermentation are crucial in sustaining ecological homeostasis in the gut, principally through stimulating the release and management of peptides throughout the gut [12]. In one study, more than 20 strains were screened and divided into *Lactobacillus* and *bifidobacterium* according to strain. The role of probiotics in regulating intestinal environment was further discovered by studying their ability to regulate metabolism and restore the efficiency of internal environmental homeostasis [12]. The experimental results showed that, in assisting the maintenance of intestinal homeostasis, both probiotics increased the expression of glucagon-like peptide-1 (GLP-1) and interleukin-10 (IL-10) in T2DM patients, inhibited the accumulation of lipids in adipocytes, and improved body metabolism.

At the same time, as a beneficial component of human intestinal flora, probiotics not only improve the host's serum metabolomics, regulate the body's energy metabolism and intestinal PH, but also improve the insulin sensitivity of T2DM patients [13]. For example, T2DM patients were treated for 5 weeks using *Lactobacillus fermentans* MCC2759 and MCC2760 as starter cultures. It was found that the body weight changed after taking *Lactobacillus fermentum*, which may be due to the disappearance of weight-related structural proteins under the influence of probiotics that lead to weight loss. On the other hand, *Lactobacillus fermentans* can increase the expression of glucose transporters GLP-1 and ZO-1, which makes the receptors more sensitive to insulin recognition, thus increasing the glucose transport efficiency and improving glucose tolerance of mice given a diet high in fat [13].

## 3. Conclusion

By summarizing the existing research results of probiotics in the treatment of T2DM, it can be found that probiotics are applicable and innovative in the intervention of T2DM, and give full play to the advantages in multiple aspects, such as regulating FBG and insulin levels by improving intestinal inflammation and oxidative stress, controlling and strengthening body metabolism and insulin sensitivity, etc. In combination with other drugs, probiotics can also play a certain potential of adjuvant therapy. In addition, most probiotics use non-injectable means, which can provide convenience for treatment and realize simple operation of patients. Therefore, the treatment of T2DM with probiotics provides a good development idea for the field of diabetes treatment and provides a theoretical basis and research direction for further research.

Despite that, the prevailing inquiries remains full of flaws and inadequacies. Firstly, in many studies, the types of probiotics used are very complicated, and there is no clear classification and systematic exploration, which may lead to unstable experimental results when different strains are used. Secondly, the administration dose and test period of probiotics were not uniform, resulting in high heterogeneity of experimental results. Finally, from the case of probiotic combination therapy, it can be found that probiotics did not play the maximum role in the treatment of T2DM, and more

exploration experiments are needed in the future to improve this system. Therefore, in the future, Chinese researchers can conduct in-depth studies on the mechanism regulation, pathophysiology, pathway and other aspects related to probiotics and T2DM, explore the research effects brought by different types of probiotics and different doses, improve theoretical studies, promote the output of high-quality results, and provide more convenient individualized treatment programs that are beneficial to patients.

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