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The Application and Research of Probiotics in the Treatment of Diabetes

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Abstract: ***This review explores the application and research progress of probiotics in the treatment of diabetes. With the rising incidence of diabetes, traditional treatments face numerous challenges, including side effects of medications and poor patient compliance. As a novel therapeutic approach, probiotics have shown potential in improving glycemic control, enhancing insulin sensitivity, and lowering inflammation levels. Research indicates that probiotics can regulate the gut microbiome, improve intestinal barrier function, promote nutrient absorption, and thus affect overall metabolic status. Furthermore, the antioxidant properties of probiotics have shown positive effects in protecting pancreatic cells and alleviating diabetes complications. Recent clinical trials have further supported the application of probiotics in diabetes management, especially in improving renal function, neuropathy, and cardiovascular health. Despite the optimistic results of existing studies, more high-quality randomized controlled trials are needed to establish the specific effects and optimal use strategies of different probiotics. This review provides a theoretical basis for future research and emphasizes the importance and potential of probiotics in the treatment of diabetes.***

Keywords: Probiotics; Diabetes; Gut microbiome; Complications of diabetes.

1. INTRODUCTION

Diabetes mellitus is one of the major global public health challenges. According to the 2021 report of the International Diabetes Federation (IDF), the number of people with diabetes in the world has reached 537 million and is expected to increase to 640 million by 2030[1]. Diabetes is classified into type 1 diabetes (T1DM), type 2 diabetes (T2DM), gestational diabetes and other specific types, including those caused by genetic defects, endocrine diseases, drugs or chemicals[2]. In type 1 diabetes, which usually occurs in adolescents and children, autoimmune destruction of pancreatic beta cells results in absolute insulin deficiency. Type 2 diabetes is more common in adults, mainly due to insulin resistance and relative insufficient insulin secretion. Typical symptoms of diabetes include polyuria, thirst, fatigue and weight changes. Long-term hyperglycemia can lead to a variety of complications, such as cardiovascular disease, diabetic nephropathy, retinopathy and peripheral neuropathy[3, 4]. The current treatment methods mainly include insulin therapy, oral hypoglycemic drugs (such as metformin, sulfonylureas) and lifestyle intervention. However, there are also problems with these methods. For example, insulin therapy may cause hypoglycemia, whereas oral agents may trigger gastrointestinal complaints or weight gain[4]. Metformin is the drug of choice for the treatment of type 2 diabetes but can cause gastrointestinal discomfort such as nausea, vomiting, and diarrhea, and studies have shown that metformin can worsen acute kidney injury[5]. A common side effect of sulfonylureas is hypoglycemia, especially when combined with other antidiabetic agents. In addition, patients may experience weight gain and allergic reactions such as rash and pruritus[6]. Insulin-sensitizing agents often cause edema and weight gain, especially in high-risk patients, and they may also increase the risk for heart failure[7]. DPP-4 inhibitors commonly cause nasopharyngitis and gastrointestinal discomfort, and in rare patients, acute pancreatitis may occur[8]. SGLT2 inhibitors and GLP-1 receptor agonists may cause an extremely rare serious adverse effect of pancreatitis[9]. Diabetic patients may discontinue treatment due to drug side effects, which directly affects the management of the disease and the quality of life of patients. In this context, probiotics, as an emerging treatment strategy, has gradually attracted attention.

2. PROBIOTICS

As a kind of live microbial probiotics, which are widely used in food and beneficial to human health, probiotics can improve blood glucose, reduce insulin resistance, enhance immune function and reduce inflammation level by regulating intestinal flora[10]. Common probiotics include lactic acid bacteria (e.g., Lactobacillus acidophilus) and Bifidobacteria (e.g., Bifidobacterium longum), which are able to improve the balance of the gut microbiota through multiple mechanisms. Probiotics are mainly derived from fermented foods, such as yogurt, pickles, tempeh, etc. Probiotics have a variety of biological properties, such as enhancing intestinal barrier function, regulating immune response, anti-inflammation, and anti-oxidation[11]. Studies have shown that probiotics can

promote the production of short-chain fatty acids and improve the intestinal environment. For example, Lactobacillus rhamnosus GG has been shown to reduce intestinal permeability, thereby effectively reducing the risk of metabolic syndrome[12]. Compared with traditional drugs, probiotics have relatively few side effects and can be safely tolerated by most people. This is particularly important for patients who need long-term management of diabetes. At the same time, probiotics can improve the balance of intestinal microbiota, promote nutrient absorption and energy metabolism, maintain normal blood glucose levels, and reduce the level of chronic inflammation in the body by enhancing the intestinal barrier and regulating the immune response[13]. With the increasing health awareness, the market for probiotic food is also growing rapidly. This innovative treatment modality can not only reduce the side effects of traditional drugs, but also improve patient compliance and improve their quality of life.

3. 3.CURRENT APPLICATION AND RESEARCH OF PROBIOTICS IN THE TREATMENT OF DIABETES

3.1 Regulates absorption and utilization of nutrients and energy

A persistent state of hyperglycemia may impair intestinal function, thereby affecting the digestion and absorption of nutrients, leading to malnutrition. At the same time, the intestinal microbiota of diabetic patients is often unbalanced, which interferes with the metabolism of nutrients and reduces the production of short-chain fatty acids. Insulin resistance can affect the efficiency of cells to use nutrients, especially glucose, leading to disorders of energy metabolism[14]. Diabetes may also lead to increased intestinal permeability and impair intestinal barrier function, thereby affecting normal nutrient absorption[15].

By improving the balance of intestinal microbiota, probiotics can affect the digestion, absorption and metabolism of nutrients, thereby enhancing the energy utilization rate of the host. Lactobacillus acidophilus was found to improve the efficiency of intestinal metabolism of carbohydrates[16]. One study showed that patients with Lactobacillus acidophilus supplementation had a significant reduction in blood glucose levels, which may be related to the enhanced ability of the intestine to absorb glucose[17]. This finding suggests that probiotics not only improve glycemic control but may also improve the overall metabolic profile by enhancing nutrient absorption. Bifidobacteria have been found to promote gut health by producing short-chain fatty acids (SCFAs), such as acetate and butyrate. These SCFAs are not only a major energy source for intestinal epithelial cells, but also contribute to fatty acid oxidation and energy production[18]. In addition, lactic acid bacteria showed positive effects on energy metabolism, and related studies found that lactic acid bacteria supplementation was able to significantly reduce body weight in obese mice while increasing their metabolic rate. Researchers believe that this is related to the ability of lactic acid bacteria to promote the growth and activity of beneficial microbes in the gut, thereby improving energy utilization. Probiotics also play a key role in promoting the diversity of the gut microbiota[19]. Probiotics not only rely on the effect of a single strain in regulating the absorption and utilization of nutrients and energy, but also may achieve better effects through synergistic effects.

3.2 Improve intestinal barrier function

Gut barrier function is essential for the maintenance of systemic health, and its main role is to prevent harmful substances and pathogens from entering the bloodstream while allowing for efficient absorption of nutrients. Patients with diabetes often face reduced intestinal barrier function, which can lead to intestinal leakage and chronic inflammation. Probiotics have been widely studied to improve the intestinal barrier function and enhance its defense capacity. Probiotics can improve the intestinal barrier by promoting the tight junctions of intestinal epithelial cells. Tight junctions are structures between intestinal epithelial cells that form a barrier by connecting to each other to restrict the passage of substances[20]. Lactobacillus acidophilus can increase the expression of tight junction proteins in intestinal epithelial cells, thereby enhancing the integrity of the intestinal barrier. Lactobacillus acidophilus supplementation may help reduce the incidence of intestinal leaks and improve gut health[21]. Lactobacillus casei CCFM419 could increase the expression of intestinal tight junction proteins (such as occludin and ZO-1), improve intestinal barrier function, reduce intestinal permeability, and thus alleviate insulin resistance in type 2 diabetic mice[22]. Lactobacillus casei Zhang can increase the expression of tight junction proteins (such as claudin-1, occludin and ZO-1), reduce intestinal permeability and inflammation, improve intestinal barrier function, and reduce blood glucose level in type 2 diabetic rats.

3.3 Regulates the host immune response

Persistent hyperglycemia leads to oxidative stress in the body, which in turn damages cells and tissues, activates the immune system, and triggers a chronic inflammatory response. The gut microbiome is unbalanced, leading to the proliferation of harmful bacteria, which further stimulates the immune system and exacerbates inflammation[23]. Probiotics activate the local immune system by interacting with intestinal epithelial cells and increase the number and activity of immune cells such as gut associated lymphoid tissue (GALT). Studies have shown that probiotics can promote the proliferation and differentiation of immune cells such as T cells and B cells, thereby enhancing the body's defense against pathogens[24, 25]. Many probiotics produce short-chain fatty acids (SCFAs), cytokines, and other immunomodulatory factors that modulate the immune response. For example, SCFAs can inhibit the production of proinflammatory cytokines and reduce systemic inflammation. Probiotics reduce the growth of harmful microorganisms through competitive exclusion and direct inhibition. This mechanism helps to maintain the balance of gut microbes, thereby reducing the risk of infection and inflammation[26]. Lactobacillus rhamnosus has been found to stimulate the activity of macrophages, enhance antibody production, and promote the activation of T cells, thereby enhancing the immune response[27]. Although not a traditional probiotic, Prashiella sp., is thought to have a probiotic effect. Studies have shown that it can produce anti-inflammatory metabolites, promote the differentiation of regulatory T cells, reduce inflammation, and thus improve the symptoms of diabetes[28]. Bifidobacterium animalis 420 has shown potential to improve metabolic syndrome and diabetes-related indicators. It is able to reduce intestinal permeability, reduce the level of inflammation, regulate the immune response, and improve insulin resistance[29]. Lactobacillus fermentans has shown potential to improve diabetes by modulating intestinal immune responses, promoting differentiation of regulatory T cells, reducing inflammation, and improving insulin resistance and blood glucose levels[30].

3.4 Antioxidation

The antioxidant properties of probiotics play an important role in protecting pancreatic cells, which, especially islet β cells, are responsible for insulin secretion and regulate blood glucose levels. However, hyperglycemia and oxidative stress can cause damage to islet β cells, affect their function, and even lead to apoptosis[31]. Probiotics exert antioxidant effects through a variety of mechanisms. First, they are able to produce short-chain fatty acids (SCFAs) and other metabolites, which have significant antioxidant properties and are able to neutralize free radicals and mitigate oxidative damage. For example, SCFAs produced by Lactobacillus and Bifidobacterium in the gut can reduce systemic oxidative stress levels by improving the intestinal microenvironment[32, 33]. Probiotics can also enhance the antioxidant capacity of cells by regulating the antioxidant enzyme system of the body. Studies have shown that Lactobacillus acidophilus, Lactobacillus rhamnosus, and Bifidobacterium longum are able to stimulate the expression of antioxidant enzymes, such as superoxide dismutase (SOD) and glutathione peroxidase (GPx), which play a key role in the removal of harmful oxidative substances from the body[34]. Lactobacillus fermentans has significant antioxidant activity, which can inhibit the generation of free radicals and reduce oxidative stress levels and protect cells from oxidative damage. By inhibiting the release of proinflammatory cytokines, probiotics are able to reduce the inflammatory response, thereby mitigating the damage to pancreatic cells[35]. The antioxidative and hypoglycemic effects of Streptococcus lactis on streptozotocin-induced diabetic rats were studied. The results showed that Streptococcus lactis could significantly increase the activity of antioxidant enzymes in pancreatic tissue, reduce oxidative stress level, and protect pancreatic β-cell function[36, 37].

4. RESEARCH PROGRESS ON CLINICAL TRIALS OF PROBIOTICS

In recent years, several clinical trials have evaluated the use of probiotics in patients with diabetes. Multiple clinical trials have shown that supplementation with specific probiotics such as Lactobacillus acidophilus and Bifidobacterium can significantly reduce fasting blood glucose and glycosylated hemoglobin (HbA1c) levels in diabetic patients[38]. Clinical trials have found that Bifidobacteria supplementation can significantly improve insulin sensitivity by improving the composition of the gut microbiome and promoting the production of short-chain fatty acids. Many clinical trials have highlighted the role of probiotics in modulating immune responses and lowering inflammatory markers (e.g., C-reactive protein, tumor necrosis factor, α), which is particularly important for diabetes management. Probiotic supplementation can improve the gut microbiota of diabetic patients and increase the abundance of beneficial flora. Not only does this aid digestion and absorption, but it may also improve the overall metabolic state[39]. Probiotics have been studied in combination with other treatments, such as medications and dietary interventions, to enhance the effects of these treatments and further improve blood sugar control and metabolic health. Probiotic supplementation may help reduce symptoms of diabetes complications and improve patients' quality of life[40]. Studies have found that supplementation with probiotics such as bifidobacteria can improve kidney function and reduce urine protein levels in diabetic patients,

and patients in the probiotic group have significant improvement in renal function indicators[41]. Lactobacillus acidophilus supplementation can improve nerve function and reduce pain and discomfort in patients[42]. Streptococcus lactis is able to reduce cardiovascular risk in diabetic patients by improving metabolic health and lowering inflammatory responses, with significantly lower blood lipid levels and inflammatory markers[43]. Despite the positive results of existing studies, more high-quality randomized controlled trials are needed to establish the specific effects, optimal dose, and duration of treatment of different probiotics. Future research will contribute to a deeper understanding of the potential of probiotics in diabetes management and provide stronger evidence support for clinical applications.

5. CONCLUSIONS AND OUTLOOK

Probiotics have shown promise in the treatment of diabetes, with studies showing their ability to improve patients' metabolic status through a variety of mechanisms. However, more research is needed to confirm the optimal combination and dosage of different probiotics to achieve personalized treatment regimens. In the future, probiotics may become an integral part of diabetes management.

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