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The Impact of Probiotics on Glucose Metabolism and Intestinal Barrier Function in Elderly Patients with Type 2 Diabetes Mellitus

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Abstract:

With the global aging process accelerating, the prevalence of elderly Type 2 Diabetes Mellitus has increased significantly. There are approximately 35 million elderly Type 2 Diabetes Mellitus patients in China aged over 65. The imbalance of intestinal flora (decrease in probiotics and increase in conditional pathogens) and intestinal barrier damage in these patients deteriorate the disease through a "flora-barrier-metabolism" vicious circle. However, systematic reviews of probiotics targeting this population are still lacking. This study explores the effects of probiotics on elderly Type 2 Diabetes Mellitus patients systematically. The results show that probiotics can improve glycometabolic indicators (such as fasting blood glucose and insulin resistance) by constructing an intestinal mucosal barrier and regulating the activity of enzymes related to glucose and lipid metabolism. They can also optimize the intestinal flora structure by increasing the content of short-chain fatty acids and repair the intestinal barrier by promoting the secretion of mucin MUC2 to increase the mucus layer. There are limitations such as significant strain specificity and unclear optimal dosage and combination. In the future, large-sample trials combined with multi-omics technology are needed to provide a basis for precise microecological intervention.

Keywords: Elderly type 2 diabetes mellitus; probiotics; intestinal flora imbalance; intestinal barrier repair; glycometabolism.

1. Introduction

As the global aging process accelerates, the incidence of Type 2 Diabetes Mellitus (T2DM) among the elderly has risen sharply, leading to a substantial prevalence increase. Approximately 537 million adults

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worldwide suffer from diabetes, among whom T2DM accounts for more than 90%. The global prevalence of elderly T2DM in people over 65 years old is estimated to have exceeded 20%. China has the largest number of elderly T2DM patients in the world, with an estimated 35 million elderly people aged 65 and above suffering from T2DM [1]. Affected by the aggravation of population aging and lifestyle changes, the number of this population is still growing year by year. T2DM is a chronic metabolic disease characterized by hyperglycemia, which is caused by insulin resistance (IR) and defective insulin secretion by pancreatic β-cells.

Elderly T2DM refers to T2DM that occurs in old age or develops in young and middle age and then persists into old age. With age increasing, physical functions declining, the insulin sensitivity of muscles and liver in elderly patients also decreases. Meanwhile, the function of pancreatic β-cells declines, and the reduction of physical activity in the elderly further aggravates insulin resistance. Elderly T2DM is often accompanied by a variety of complications, including gastrointestinal disorders, intestinal flora imbalance and intestinal barrier damage. These complications themselves are also important factors inducing insulin resistance and chronic low-grade inflammation [2].

The investigation has illustrated that there are significant differences in intestinal flora between elderly T2DM patients and healthy elderly people. This imbalance is often manifested by a decrease in probiotics (such as Bifidobacterium and Lactobacillus) and an increase in opportunistic pathogens (such as Escherichia coli and Enterococcus) in the intestinal tract of the elderly [3]. This occurrence of this phenomenon is related to the disorder of glucose metabolism in patients. For example, the disorder of glucose metabolism in elderly T2DM patients changes the intestinal microecology (such as pH value, oxygen concentration, and carbohydrate composition ratio), making probiotics sensitive to environmental changes, making it more difficult to survive [3]. Metabolic disorders of elderly T2DM patients themselves also affect the intestinal ability to clear pathogenic bacteria. In addition, the immune function of diabetic patients is weaker than that of healthy people, and their resistance to common pathogens is reduced accordingly, leading to an increase incommon pathogens. Intestinal flora imbalance causes intestinal barrier damage, and finally forms a "flora-barrier-metabolism" vicious cycle. Therefore, changing the gastrointestinal microecological environment of elderly T2DM patients is gradually becoming a new therapeutic target.

A number of studies have shown that probiotics can actively regulate the intestinal microecology, whether as an adjuvant treatment for hypoglycemic drugs or as an independent intervention measure. Supplementing probiotics has been proven to improve the glycometabolism of elderly T2DM patients (such as reducing glycosylated hemoglobin and fasting blood glucose), repair the intestinal barrier, and alleviate gastrointestinal symptoms [4]. However, there is still a lack of systematic reviews specifically targeting the elderly T2DM population. Key problems such as the efficacy of probiotics used alone or in combination with drugs, strain specificity, and the optimal dose-effect relationship remained unknown.

Therefore, this study aims to systematically elaborate the effects of probiotics on the glycometabolism and intestinal barrier function of elderly T2DM patients, summarize recent research results, explore their potential mechanisms, and provide nutritional intervention strategies and expected references for future development.

2. Elderly T2DM patients with Intestinal Flora Imbalance and Intestinal Barrier Damage

2.1 Epidemiological and Metabolic Characteristics of Elderly T2DM

The epidemic situation of elderly T2DM shows a trend of rapid growth globally and significant growth in China. According to the data released by the International Diabetes Federation (IDF) in 2023, about 537 million adults worldwide suffer from diabetes, of which T2DM accounts for more than 90%. The global prevalence of elderly T2DM in people over 65 years old is estimated to have exceeded 20%. China has the largest number of elderly diabetic patients in the world. An epidemiological survey in 2020 showed that the number of elderly people with diabetes aged 60 and above in China is expected to exceed 35 million, and this number is still increasing with the aging tendency of the population [4].

The physiological mechanism and clinical characteristics of elderly T2DM have unique metabolic complexity. Insulin resistance as well as β-cell function decline are the main characteristics of elderly T2DM. With the growth of age, the sensitivity of muscles, liver and other tissues to insulin decreases. In addition, the elderly often have abdominal obesity and reduced physical activity, leading to weakened metabolic ability, which further aggravates insulin resistance. The function of pancreatic islet β-cells declines naturally, with a decrease in the ability to secrete insulin. Under the heavy burden of insulin resistance, the function of β-cells exhausts more rapidly, which is characterized by prominent postprandial hyperglycemia. Due to the distinct reduction of the rapid response ability of β-cells to blood glucose elevation, postprandial blood glucose in-

creases much more obviously in elderly patients. Elderly patients often suffer from multiple complications such as hypertension, dyslipidemia, coronary heart disease, chronic kidney disease and frailty, and need to take a variety of drugs, contributing to the high complexity of treatment [4].

2.2 Intestinal Flora Imbalance and Intestinal Barrier Damage in Elderly T2DM

Insulin resistance, glucose and lipid metabolism disorders, and systemic inflammatory response are the main pathological characteristics of T2DM patients. The imbalance of intestinal microenvironment is closely related to the occurrence, development and insulin resistance of T2DM. Intestinal flora can regulate the immune system and inflammatory response, adjust the integrity of the intestinal barrier and human metabolism, and participate in the synthesis of metabolites. However, the intestinal flora of elderly T2DM patients is characterized by a decrease in beneficial bacteria and an increase in conditional pathogens, which leads to intestinal flora disorder. Due to the decrease of probiotics in elderly T2DM patients, the synthesis of short-chain fatty acids (SCFAs) is reduced as well. The production of SCFAs is helpful to enhance the integrity of intestinal barrier, promote the proliferation of pancreatic β-cells and the synthesis of insulin, so the reduction of SCFAs leads to intestinal barrier damage. Flora disorder also impairs the production of other metabolites, such as branched-chain amino acids and trimethylamine, which destroys glucose homeostasis and further causes T2DM [5]. At the same time, opportunistic pathogens stimulate the local immune system, change intestinal permeability, lead to pathological intestinal leakage, and then activate systemic inflammation, finally leading to insulin resi stance.

3. Effects and Mechanisms of Probiotics on Improving Glycometabolism

3.1 Improvement of Blood Glucose Regulation Indicators

In the elderly T2DM population, the improvement effect of probiotics on blood glucose regulation indicators is achieved through the synergy of multiple pathways. Studies have shown that probiotics can improve blood glucose regulation indicators in different ways. First, they can form a biological immune barrier on the intestinal mucosa, maintain the balance of intestinal flora, reduce chronic low-grade inflammation and oxidative stress, and at the same time enhance the body's immune function, reduce insulin resistance and repair the oxidative damage of pancreatic β-cells to regulate blood glucose. Second, probiotics can regulate the activity of enzymes related to glucose and lipid metabolism, produce substances such as bacteriocins to protect islets and inhibit α-glucosidase, so as to delay the absorption of carbohydrates. The active peptides produced during the proliferation process inhibit the activity of postsynaptic neurons through the brain-gut axis, regulate the homeostasis of glycometabolism, and jointly regulate the fluctuation of fasting and postprandial blood glucose in elderly T2DM patients and improve metabolism.

3.2 Regulation of Intestinal Flora Structure

The ecological balance of intestinal microbiota is an important factor in maintaining human homeostasis. For elderly T2DM patients, intestinal flora imbalance is one of the factors affecting the disease course. Studies have confirmed that probiotics can colonize the human intestinal tract and regulate the structure and function of intestinal flora in a variety of ways. On the one hand, probiotics improve the intestinal barrier function, reduce the leakage of harmful substances such as lipopolysaccharides, and at the same time increase the abundance of SCFA-producing bacteria and the content of SCFAs, which can inhibit the survival of potential conditional pathogens such as Escherichia coli and optimize the composition of flora. On the other hand, they can exert antioxidant effects, inhibit the activity of glucose absorption enzymes, regulate the activity of bile salt hydrolase and cholesterol metabolism, and form a synergistic effect with the regulation of flora structure to jointly play an anti-diabetic role. The mixed probiotic Viable Strong Lactic-acid bacteria (VSL#3) has been proven to effectively reduce the insulin resistance level and inhibit weight gain in elderly T2DM patients by changing the composition of intestinal flora [6]. The combined use of probiotics can improve the intestinal flora that produces SCFAs and has a more obvious effect on blood glucose regulation. Therefore, by optimizing the composition of intestinal flora, increasing beneficial bacteria and inhibiting harmful bacteria, probiotics provide a new strategy based on microecology for the intervention of elderly T2DM [7].

3.3 Clinical Research Evidence

Probiotics intervention can significantly reduce the fasting blood glucose of elderly T2DM patients, improve insulin sensitivity and reduce the side effects of drugs. A randomized controlled clinical study included 28 T2DM patients aged 40-75 years who received metformin. They were randomly divided into an experimental group (taking two multi-strain probiotic capsules twice a day, containing

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Lactobacillus bulgaricus, Bifidobacterium and Streptococcus thermophilus, n=14) and an observation group (taking two placebo capsules twice a day, n=14), with a treatment course of 12 weeks. The results showed that in the subgroup treated with probiotics and metformin, the fasting plasma glucose, fasting plasma insulin, insulin resistance and zonulin decreased, while insulin sensitivity increased (all $p<0.05$), but no such changes were observed in the placebo group [8]. This confirms that probiotics, as an adjuvant supplement to metformin, are of great help in improving the condition of elderly T2DM patients.

4. Effects and Mechanisms of Probiotics on Repairing Intestinal Barrier Function

Intestinal barrier damage (also known as intestinal leakage) is a key inducement of insulin resistance and chronic inflammation in elderly T2DM. Probiotics can repair the damaged intestinal barrier through multi-dimensional mechanisms and reduce chronic inflammation and insulin resistance.

4.1 Effects on Intestinal Barrier Function Markers

After probiotics intervention, the expression of Mucin 2 (MUC2) is significantly improved, and the thickness of the mucus layer increases. For example, strains such as Lactobacillus and Bifidobacterium directly promote the expression of MUC2 mRNA in goblet cells. The outer membrane protein Amuc_1100 of the special strain Akkermansia muciniphila increases the number of goblet cells through the Toll-Like Receptor 2 (TLR2) signaling pathway, and promotes the secretion of antibacterial peptides, to repair and thicken the mucus layer. The thickening of the mucosal layer strengthens the chemical barrier and reduces the direct contact between conditional pathogens and intestinal epithelial cells [9].

Probiotics and their metabolic products can regulate intestinal immune-related markers. For example, SCFAs inhibit the activity of histone deacetylase (HDAC), promote the differentiation of regulatory T cells (Treg) and inhibit the proliferation of Th1/Th17 cells. At the same time, they induce the polarization of macrophages to the anti-inflammatory M2 phenotype by activating the GPR109a receptor, and reduce the levels of pro-inflammatory factors such as IL-1β and TNF-α. Probiotics can reverse the abnormal activation of pro-inflammatory M1 macrophages and Th17 cells, and reduce the immune inflammation of elderly T2DM patients [9].

4.2 Promotion of Mucus Layer Repair Function

As a part of the innate intestinal mucosal barrier, mucus plays a role as the first line of defense by reducing the exposure of the intestinal tract to antigens and bacteria, thus resisting potentially harmful compounds. Probiotics have been proven to strengthen the intestinal barrier by regulating the synthesis of the intestinal mucus layer and the intestinal flora [9].

Short-chain fatty acids produced by probiotics are important signal molecules for mucus layer repair. They can up-regulate the expression of MUC2 gene by activating the related pathways of intestinal epithelial cells, promote the synthesis and secretion of mucin, and then thicken the mucus layer. In addition, the microbe-associated molecular patterns (MAMPs) released by probiotics, such as flagellin of Gram-negative bacteria, lysophosphatidic acid (LPA) of Gram-positive bacteria, and lipopolysaccharide (LPS), can also regulate the expression of mucin genes, increase the amount of mucus secreted by goblet cells, and synergistically strengthen the chemical barrier function of the mucus layer [10].

5. Challenges and Prospects from Research to Application

The positive effects of probiotics on the regulation of glycometabolism and the repair of the intestinal barrier in elderly T2DM patients have been confirmed, but there are still challenges in the field of clinical application. First, there is significant strain specificity. The probiotic strains, combination forms and dosages used in existing studies vary greatly, and different strains have their own advantages. Studies have shown that Lactobacillus strains have more advantages in reducing the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), while the combination of Bifidobacterium and Akkermansia muciniphila is more effective in increasing the level of SCFAs and repairing the thickness of the mucus layer [11]. Second, the safety of long-term use of probiotics is not clear. Elderly T2DM patients have weakened immune function and are accompanied by a variety of complications. Whether long-term use will inhibit native bacteria and cause dependence remains unknown. Third, the actual effect of probiotics is affected by individual heterogeneity. Due to differences in personal living habits, dietary habits and disease conditions, the benefits of probiotics vary among patients.

Future research can be carried out from the following aspects: First, conduct long-term randomized controlled trials with large samples to monitor the tolerance threshold of patients using probiotics for a long time. Second, com-

bine multi-omics analysis to construct intervention models for different flora and screen precise and effective flora and combinations. Third, promote research, development and innovation, develop probiotics in different administration forms to improve the survival rate of probiotics, and establish industrial standards to fundamentally reduce the number of probiotics with substandard quality.

6. Conclusion

This study summarizes the effects of probiotics on the glycometabolism and intestinal barrier function of elderly T2DM patients, and clarifies that intestinal flora disorder and barrier damage are the core pathological links in the occurrence and development of elderly T2DM, which form a vicious cycle through the "flora-barrier-metabolism" pathway. Probiotics can improve the glycometabolism of elderly T2DM patients in two ways: first, by constructing an intestinal mucosal barrier to reduce chronic inflammation, repair the damage of pancreatic β-cells and reduce insulin resistance; second, by regulating the activity of enzymes related to glucose and lipid metabolism to improve the fluctuation of fasting blood glucose, postprandial blood glucose and the level of glycosylated hemoglobin.

In terms of reconstructing intestinal microecology, probiotics improve intestinal metabolic function by increasing the content of SCFAs, inhibiting the proliferation of conditional pathogens such as Escherichia coli, and reducing the inflammatory response caused by endotoxin (LPS). In terms of intestinal barrier repair, probiotics can strengthen the barrier function: they promote the secretion of mucin MUC2 and the thickening of the mucus layer to strengthen the chemical barrier, and at the same time reduce intestinal immune inflammation with the help of SCFAs, forming a positive regulation of "flora-barrier-metabolism".

At present, there are still limitations: there is significant strain specificity. Lactobacillus has advantages in reducing insulin resistance, and the combination of Bifidobacterium and Akkermansia muciniphila is more effective in repairing the mucus layer, but the optimal strain combination has not been determined. Key issues, such as the dosage threshold of probiotics intervention and treatment, have not been clarified.

Future research breakthroughs should include: conducting large-sample, multi-center randomized controlled trials to clarify the efficacy threshold and safety of different strains and their combinations; establishing an individualized intervention model based on flora typing by combining metagenomics and metabolomics technologies; in-depth analysis of the core signaling pathways of probiotics regulating the "intestinal barrier-glycometabolism", to provide more sufficient theoretical support and clinical basis for the precise microecological intervention of elderly T2DM.

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