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Progress in the application of intestinal flora in the treatment of diabetes

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Abstract: Intestinal flora is closely related to human health, and its imbalance is related to the occurrence and development of many diseases, such as intestinal inflammation, intestinal tumors, obesity, diabetes, autoimmune diseases, etc. It has a great effect on host nutrition, exogenous and drug metabolism, and the interaction between intestinal flora and host ensures the health of body function, and also affects the participation in various physiological activities and functions of the body.

1. Introduction

Intestinal flora is the microbial community living in the human gut, mainly composed of bacteria, fungi, viruses and other microorganisms. They play a variety of important physiological functions in the human body, and play an important role in the intake of energy and nutrition, such as helping digestion and absorption, synthesizing nutrients, regulating immunity, and maintaining intestinal health. Imbalance of intestinal flora can lead to metabolic endotoxemia, high intestinal permeability and low inflammation, all of which are associated with diabetes [1]. However, a high firmicutes/Bacteroidetes ratio has been found in diabetic patients and animals, leading to the dysfunction of certain substances, such as lipopolysaccharide (LPS) damage to the intestinal barrier, so the study of intestinal flora is of great importance for type 2 diabetes [2].

In recent years, a large number of studies have pointed out that intestinal flora is involved in energy metabolism, which is closely related to the occurrence and development of T2DM. Changes in intestinal flora are important factors in the occurrence and development of T2DM. It is generally believed that the occurrence of T2DM is one of the results of intestinal microbial disorders caused by nutrient-excess diet, such as excessive intake of salt, sugar and fat.

The imbalance of the intestinal flora in diabetic patients leads to the destruction of the diversity and stability of the flora, for example, the reduction of beneficial flora or the enhancement of harmful and conditioned pathogenic flora can induce low-grade chronic inflammation of the gut. Compared with normal people, the number of bifidobacterium and clostridium in the intestinal flora of diabetic patients decreased significantly, while the number of bacteroides and β-proteobacterium increased significantly, and the ratio of bacteroides/Firmicutes and firmicutes/clostridium were positively correlated with blood glucose level [3,4]. It was found that healthy subjects had higher levels of butyric-producing bacteria, such as Clostridium, Eubacillus rectalis, and Felicia prevotelli, while the levels of opportunistic bacteria, such as Bacteroides, Escherichia coli, and Vibrio

sulphuris, increased sharply in diabetic patients[5].

2. Application of intestinal flora in the treatment of diabetes

The treatment of diabetes based on the regulation of intestinal flora can provide innovative ideas for the prevention and treatment of diabetes. In recent years, numerous studies have been carried out on the treatment of diabetes based on the exploration of intestinal flora. The application of intestinal flora in the treatment of diabetes is introduced in the following paragraphs from four aspects: traditional Chinese medicine (TCM) ingredients, traditional Chinese medicine compounds, commonly used chemicals or biological agents and lifestyle.

2.1 TCM Ingredients

Mulberry leaf ethanol extract (MLE) can effectively improve glucose uptake and insulin resistance by regulating AMPKPGC-1α signaling pathway, inhibit α-glucosidase activity and reduce blood glucose level in diabetic mice. Studies have found that mulberry leaf extract can significantly reduce the relative abundance of actinobacteria and bifidobacteria, and increase the abundance of Bacteroidetes and proteobacteria to improve intestinal flora [6].

The extract of Berberis gansuensis bark (BK), an active anti-diabetic drug, can significantly reduce the blood glucose, improve insulin resistance and inflammation, and increase insulin sensitivity in T2DM rats. Studies have shown that BK extract can increase Bacteroides/Firmicutes ratio and Akkermansia abundance in type 2 diabetic rats, and reduce the number of harmful bacteria such as enterococcus and Clostridium. However, BK extract could not maintain its pharmacological effect on T2DM rats even when antibiotics interfered with intestinal flora, possibly because antibiotics destroyed some bacteria that could play a hypoglycemic role [7].

The main active components of Lycium berry leaves (LLB) are polysaccharides, phenolic acids and flavonoids. LLB extracts can regulate AMPK signaling pathway and PI3K pathway to improve diabetic nephropathy, regulate lipid metabolism, improve insulin resistance activity, anti-hyperglycemia and prevent diabetic complications. Studies have found that compared with T2DM rats, LLB extracts are more effective. The intestinal flora disorder of T2DM rats treated with LLB was reversed [8].

2.2 TCM Compounds

Astragalus Decoction (JSD), which consists of Astragalus and licorice, has anti-inflammatory, antioxidant and anti-diabetic effects. Its main active ingredients are glycyrrhetinic acid, isogliquiritin and glycyrrhizic acid, etc., which can increase insulin secretion and decrease creatinine clearance rate, and reduce structural damage to kidney tissue. The experiment found that intestinal community diversity of rats in JSD group was changed. α-diversity indices such as Chao1, Ace, Shannon and Simpson indexes have been significantly improved, and the abundance of Alphaproteobacteria has significantly changed [9].

Luliu Granules (LLKL) is a new Chinese herbal compound specially used for the treatment of T2DM. LLKL is composed of Luhua flower, willow tea and saffron, which can regulate intestinal flora disorder, increase the expression of occlusive protein and maintain intestinal epithelial homeostasis. Compared with the model group, the α-diversity of LLKL group increased significantly, and its diversity was closer to that of the control group. The OTU atlas analysis of β-diversity also found that compared with the model group, the intestinal community structure of LLKL group was closer to that of the control group, and the abundance of Bacteroides increased, while the proportion of firmicutes decreased [10].

Qijian Mixture (QJM), a new Chinese herbal compound, consists of Astragalus, Eubrium, Coptis and Pueraria, which has the effect of reducing blood sugar and improving diabetic nephropathy. Kuo et al. [11] compared the dominant species of intestinal flora in the control group, the model group, the QJM group and the metformin group at the phylum and genus level, and found that the intestinal flora in both the QJM group and the metformin group had a reverse effect, which could reduce the production of intestinal cytokines, enhance anti-inflammatory cytokines, and mainly increase the number of intestinal bacteroides. It can induce the enrichment of beneficial bacteria and reduce the synthesis of glucagon-like peptide 2 (GLP-2), thus achieving the therapeutic effect of T2DM. Different doses of QJM have different remission degrees on T2DM and different regulation degrees of intestinal flora, which confirms the therapeutic effect of intestinal flora on T2DM.

Liuwei Dihuang pill is composed of cooked rehmannia, dogwood, Moutan bark, yam, poria and Zexie. It has the effect of treating diabetes, hypertension, menopause and systemic lupus erythematosus. Its main active ingredients are paeonol, 23-acetyl salevol B, pachymaric acid and ursolic acid, which can reduce blood glucose and blood lipid based on SCFAs-GPR43/41-GLP-1 pathway, and enhance immunity [12]. Liuweidihuang pill can increase the SCFAs levels of acetic acid, propionic acid and butyric acid, and increase the abundance of lactobacillus, Allobaculum and ruminococcus in Firmicutes, so as to reduce T2DM symptoms [13].

2.3 Commonly used chemicals or biological agents

Not only has the hypoglycemic mechanism of Chinese medicine ingredients and Chinese medicine compounds been gradually confirmed to be related to intestinal flora, but many western medicine related studies have also confirmed that their hypoglycemic mechanism is closely related to intestinal flora.

Metformin can change the genus level of intestinal microbiota to a large extent, which can increase the ratio of Bacteroides/Firmicutes, which is considered as a metabolic marker, increase the abundance of actinomycetes, and decrease the abundance of Noranococcaceae and unclassified Ruminococcaceae [14, 15].

Studies confirmed that alpha-glucosidase inhibitor acarbose increased the relative abundance of lactobacillus and bifidobacterium in intestinal flora and consumed bacterioid bacteria, thus improving the degree of intestinal flora disturbance in type 2 diabetes patients [16].

Flora transplantation found that the microbiome altered by dipeptidyl peptidase-4 inhibitors improved the glucose tolerance of the colonized mice, increased the abundance of Bacteroidetes, and promoted the functional transformation of the intestinal flora, especially increased the production of succinic acid [17].

The SGLT-2 inhibitor Dapaglipazine can significantly reduce serum leptin levels, decrease the ratio of Firmicutes to Bacteroidetes, increase streptococcus, decrease succinic acid, and increase SCFA butyric acid levels [18, 19].

Sitapliptin, metformin and acarbose can all reduce the abundance of Proteus, reverse the decreased ratio of firmicutes to bacteroides, and affect the intestinal microflora of type 2 diabetic rats [20]. The mechanism of hypoglycemia is closely related to the ratio of firmicutes to bacteroides. The application of intestinal flora in the treatment of diabetes can play a more important role in clinic.

2.4 Lifestyle

In addition to the effect of drugs on intestinal flora to treat diabetes, people's lifestyle also has a profound impact on intestinal flora to achieve the effect of diabetes treatment.

Low glycemic index diets such as non-starchy vegetables, whole grains and legumes have been

shown to improve HbA1c levels and body weight. Studies have shown that dietary compounds containing fiber and phytochemicals can increase the abundance of fiber degrading bacteria, degrade and reduce the number and abundance of harmful bacteria to improve the internal environment [21].D.A. Diaz-Rizzolo et al. found that the elderly in the healthy diet group had a decrease in prevotella, an increase in faecalis prai and an increase in lactobacillus, and a lower probability of T2DM [22].Not only diet, but also the type of drinking water can also affect the type of flora to a certain extent. Comparing drinking neutral water (NW) and acidic water (AW), it was found that non-obese diabetic mice in the acidic water group were more likely to develop diabetes. 16SRDNA-targeted pyrhosequencing showed that drinking neutral water contributed to the reduction of Prevotella and Bacteroides, and the increase of paracelloides and other members of Prevotella [23].Exercise should be part of the routine treatment of type 2 diabetes, aerobic exercise such as brisk walking, swimming and appropriate resistance exercises such as squats can not only exercise heart and lung function, but also effectively improve glucose metabolism to control high blood sugar. Long-term exercise in T2DM patients with stable blood glucose will significantly reduce the number of Candida albicans to improve T2DM symptoms. In addition, exercise intensity also affects the type and number of intestinal flora, and higher exercise intensity can increase the groups of bifidobacteria and Escherichia, Lactobacillus acidophilus muris and butyrate [24].

The treatment of T2DM patients is inextricably related to their lifestyle, which is closely related to the improvement of intestinal flora disorder, further confirming that the regulation of intestinal flora is of great significance for regulating body status and improving T2DM.

3. Conclusion

Intestinal flora plays an important role in the treatment of diabetes. Traditional Chinese medicine components, traditional Chinese medicine compounds, commonly used western medicines and adjustment of lifestyle can affect the balance of intestinal flora through different ways, so as to achieve the purpose of improving diabetes.

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