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WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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MINIREVIEWS

Diabetes and gut microbiota

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Abstract

The prevalence of diabetes has increased rapidly throughout the world in recent years. Currently, approximately 463 million people are living with diabetes, and the number has tripled over the last two decades. Here, we describe the global epidemiology of diabetes in 2019 and forecast the trends to 2030 and 2045 in China, India, USA, and the globally. The gut microbiota plays a major role in metabolic diseases, especially diabetes. In this review, we describe the interaction between diabetes and gut microbiota in three aspects: probiotics, antidiabetic medication, and diet. Recent findings indicate that probiotics, antidiabetic medications, or dietary interventions treat diabetes by shifting the gut microbiome, particularly by raising beneficial bacteria and reducing harmful bacteria. We conclude that targeting the gut microbiota is becoming a novel therapeutic strategy for diabetes.

Key Words: Diabetes; Gut microbiota; Epidemiology; Probiotics; Anti-diabetic medication; Diet

Core Tip: The current review describes the global epidemiology of diabetes in 2019 and forecasted the trends to 2030 and 2045 in China, India, USA, and globally. This review also summarizes the interaction between diabetes and the gut microbiota in three aspects: probiotics, antidiabetic medications, and diet.

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INTRODUCTION

The global prevalence of diabetes has grown rapidly in recent decades. Diabetes is becoming a serious global health threat, and is one of the top 10 leading causes of death among adults[1]. The etiology and progression of diabetes are commonly driven by genetic and environmental factors. The International Diabetes Federation (IDF) estimates that in 2019 there were 463 million cases of diabetes mellitus worldwide and approximately 4.2 million adults died from diabetes and its complications[2]. It is estimated that approximately 700 million adults will be diagnosed with diabetes by 2045. Diabetes mellitus is a group of metabolic diseases that cause high blood glucose, and primarily includes type 2 diabetes (T2D), type 1 diabetes, prediabetes, and gestational diabetes. T2D is the most common type of diabetes and represents approximately 90% of all diabetes patients worldwide[3].

The gut microbiota is a collective term for the intestinal microbial community, which plays a crucial role in maintaining health and disease pathogenesis. Recently, the gut microbiome has become an emerging research area for diabetes management, as gut dysbiosis directly or indirectly participates in diabetes by affecting host intestinal barrier functions and metabolic homeostasis[4]. Animal and human studies have identified related differences in the composition of the gut microbiota in patients with diabetes[5]. In this review, we describe global trends in diabetes in 2019, predict the trends to 2030 and 2045, and summarize the latest findings regarding the gut microbiota in diabetes.

EPIDEMIOLOGY OF DIABETES

Diabetes is one of the fastest growing global health challenges in the last 40 years, with the number of adults living with diabetes rising from 108 million in 1980 to 463.0 million (368.7–600.6 million) in 2019. This number is projected to reach 578.4 million (456.5–747.6 million) in 2030 and 700.2 million (540.7–904.6 million) in 2045. The global prevalence of adult diabetes increased from 4.7% in 1980 to 8.3% (6.2%–11.8%) in 2019, and is projected to reach 9.2% (6.8%–12.9%) in 2030 and 9.6% (7.1%–13.4%) in 2045[1]. Although the common long-term complications in diabetic patients develop gradually, they could be disabling or even life-threatening over time[6]. Diabetes is a major cause of many diseases, such as eye damage, kidney failure, heart and blood vessel disease, neuropathy, Alzheimer's disease, and lower limb amputation. Global diabetes-related health spending continues to grow rapidly as well. It was 760 billion US dollars in 2019, approximately 10% of total global health spending, and is expected to reach 825 billion US dollars in 2030 and 845 billion in 2045[7].

China and India were the two countries with the highest number of adult diabetic patients in 2019 and are projected to remain so in 2030 and 2045, due to the demographic and socioeconomic status factors. The IDF Diabetes Atlas (9th edition 2019) estimated the number of people with diabetes in China, India, USA, and the world in 2019, and projected that by 2030 and 2045 (Figure 1), the number of adults living with diabetes in China will increase from 116.4 million (108.6–145.7 million) in 2019 to 140.5 million (130.3–172.3 million) in 2030, and 147.2 million (134.7–176.2 million) in 2045. In India, the number of diabetes cases is projected to grow from 77.0 million (62.4–96.4 million) in 2019 to 101.0 million (81.6–125.6 million) in 2030, and 134.2 million (108.5–165.7 million) in 2045. The number of adult diabetes cases in the USA will increase from 31.0 million (26.7–35.8 million) in 2019, to a projected 34.4 million (29.7–39.8 million) in 2030 and 36.0 million (31.0–41.6 million) in 2045. Over the last 40 years, the number of people with diabetes has quadrupled throughout the world. The prevalence of diabetes will increase more rapidly in low-income than in high-income countries in the near future[1]. Unmet medical needs related to diabetes are a growing global public health problem.

INTERACTION BETWEEN DIABETES AND GUT MICROBIOTA

Observational findings from recent epidemiological, physiological and metabolomic

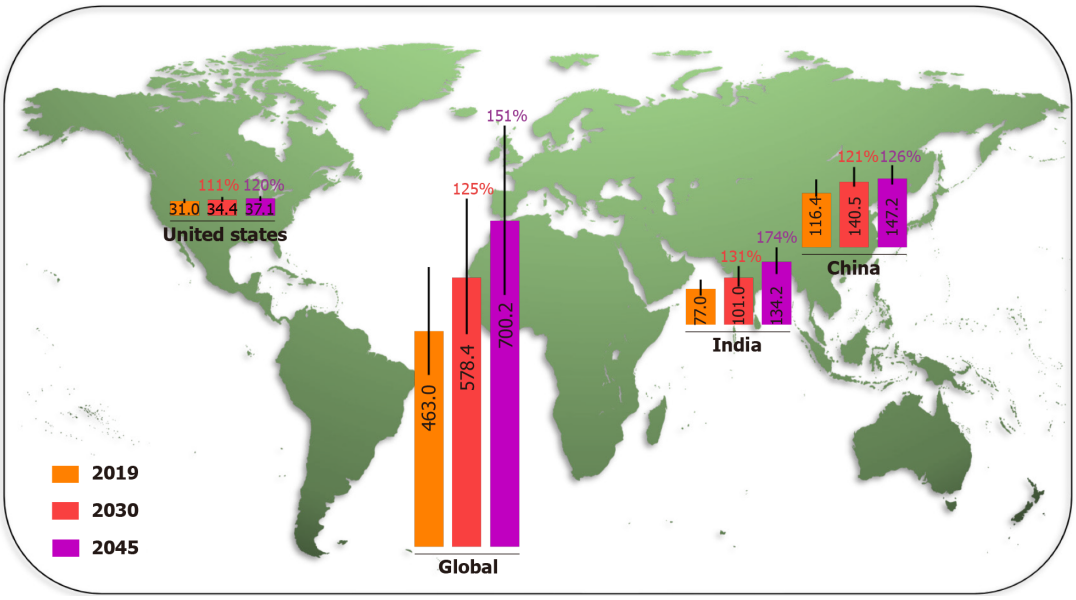

Figure 1 Millions of diabetes cases in 2019 and projections to 2030 and 2045, with projected percentage changes. Data are from the International Diabetes Federation Diabetes Atlas (9th edition 2019).

studies, complemented by cellular and animal experiments and clinical trials, it appears that microbial communities may contribute to the pathogenesis of a variety of common metabolic disorders, including obesity and diabetes, and their complications [3,8]. Although accumulative evidence suggests that the gut microbiota is a factor influencing diabetes, the underlying mechanisms remain unclear. Due to the crosstalk between the gut microbiota and host homeostasis, the gut microbiome is thought to play a crucial role in obesity and associated metabolic dysfunction[9,10]. The gut microbiome has been shown to affect host metabolism, food consumption, body weight, and glucose and lipid homeostasis. Gut dysbiosis or altered microbiota composition has been detected in obesity and diabetes in human and murine models [11]. Treatment with probiotics, antidiabetic medications, or dietary interventions can orchestrate the gut microbiome, leading to increased probiotic bacteria and decreased harmful bacteria, and these changes subsequently contribute to bodyweight loss, suppression of inflammation, and maintenance of glucose homeostasis in the host[12]. Targeting the gut microbiota is developing into a possible therapeutic strategy for diabetes.

Probiotics

Probiotics are living microorganisms that provide health benefits to their host, particularly the digestive system. Probiotics, such as *Akkermansia*, *Bacteroides*, *Bifidobacterium* and *Lactobacillus*, are currently suggested as novel and potential biotherapeutics in the prevention and management of diabetes[13,14]. Oxidative stress is a key player in the development of diabetes and diabetes-related complications[15]. Supplementation with probiotics and also synbiotics could be beneficial for patients diagnosed with diabetes also because these products lower oxidative stress levels[16,17]. Cumulative studies have proven the efficacy of probiotics in the treatment of diabetes by decreasing fasting glucose and insulin levels in animal models and clinical trials[18].

Akkermansia muciniphila is a species of mucin-degrading bacteria recently found in the human gut, and its abundance has been reported to be inversely correlated with obesity, T2D and inflammation[19-22]. Administration of *A. muciniphila* protected against high fat diet (HFD)-induced obesity and insulin resistance by suppressing inflammation and improving gut barrier function. In addition, a purified protein in the outer membrane of *A. muciniphila* called Amuc-1100 could improve metabolic syndrome in obese and diabetic mice through the Toll-like receptor 2 signaling pathway[23]. In human clinical trials, supplementation with *A. muciniphila* compared to the placebo improved insulin sensitivity, reduced insulinemia and plasma total cholesterol, and decreased body weight in overweight/obese insulin-resistant volunteers[24]. In our recent studies, we found that melatonin, a probiotic agent, partially improved insulin resistance by increasing the abundance of *A. muciniphila* in HFD-fed mice[25]. *A. muciniphila* is considered a promising probiotic to improve

diabetes and obesity-associated metabolic disorders.

Bacteroides is a common genus associated with the risk of T2D in patients. However, the role of *Bacteroides* in diabetes is controversial. Some studies have shown that the abundance of *Bacteroides* is inversely associated with diabetes risk[26-30], while others have reported a positive association in different species[31-33]. This inconsistency may be explained by the underlying feedback mechanism of the gut microbiome at different stages of the disease or in different animal models. The ratio of Bacteroidetes to Firmicutes, previously identified as a marker for metabolic diseases, does not seem to be consistently associated with diabetes risk[14]. In animal studies, treatment with *Bacteroides acidifaciens* and *Bacteroides uniformis* prevents obesity and improves insulin susceptibility in diabetic mice[34,35]. These studies suggest that *Bacteroides* may have a beneficial effect on diabetes.

Bifidobacterium, also known as *Lactobacillus bifidus*, is frequently reported in T2D protection studies. *Bifidobacterium* strains are crucial probiotics in the dairy industry, due to their unique function of fermenting carbohydrates *via* the fructose-6-phosphate phosphoketolase pathway[36]. Numerous studies have shown that *Bifidobacterium* has beneficial effects on glucose tolerance in individuals with T2D and diabetic murine models[37-39]. Oral administration of *Bifidobacterium* decreases blood glucose concentration and glycosylated hemoglobin levels, and improves lipid profiles, insulin resistance, and antioxidant indexes, through insulin receptor substrate/phosphoinositide 3-kinase/protein kinase B and kelch-like ECH-associated protein 1/nuclear factor erythroid 2-related factor 2 signaling pathway in murine diabetic models[40]. *Bifidobacterium* may be a promising probiotic to treat diabetes.

Lactobacillus is the most commonly used probiotic in industry to control food fermentation, such as yogurt, cheese, wine, and other fermented foods. Studies of the composition of gut microbiota showed some species in this genus were increased in T2D patients, such as *Lactobacillus acidophilus*, *Lactobacillus gasseri* and *Lactobacillus salivarius*, whereas *Lactobacillus amylovorus* was decreased in patients with diabetes[41-43]. Oral supplementation of *Lactobacillus*, such as *Lactobacillus casei*, *Lactobacillus curvatus*, *L. gasseri*, *Lactobacillus paracasei*, *Lactobacillus plantarum*, *Lactobacillus reuteri*, *Lactobacillus rhamnosus* and *Lactobacillus sakei*, exhibited beneficial effects in diabetic mice and individuals with diabetes[44-54]. The antidiabetic mechanism of *Lactobacillus* by inhibiting endotoxin secretion and activating G-protein-coupled receptor 43 pathway has been reported[55]. The combination of *Lactobacillus* and *Bifidobacterium* is widely used in clinical practice to synergistically maintain a healthy digestive tract. Growing evidence supports that probiotics are a safe and effective treatment strategy under certain clinical conditions of diabetes.

Diet

Diet is an essential regulator of the gut microbiome[56]. Interactions between diet and gut microbiota have been reported to affect obesity, insulin resistance, and the chronic inflammatory response of the host[57]. Here, we mainly summarize the roles of diet in the gut microbiome and diabetes.

Diet composition is vital in diabetes development. Diabetes was considered a disease of the rich, because of its high prevalence among the rich who access food more easily, including flour, sugar, fat and meat[58]. It has been shown that diets with high levels of sugar, fat and cholesterol increase the risk of diabetes. These diets cause gut dysbiosis and damage the intestinal mucosal barrier that facilitates the development of diabetes[59,60]. High-fiber diet is a well-known healthy diet with various benefits, such as improving bowel movements, lowering cholesterol, achieving a healthy weight, and controlling blood sugar levels. Dietary fibers consist of cellulose, resistant starch and dextrin, inulin, lignin, pectin, -glucan, and oligosaccharides. They are abundant in whole-grain bread and cereals, legumes, rice, vegetables and fruits, and cannot be completely digested or absorbed by the human digestive system[61,62]. Dietary fibers play an essential role in maintaining the gut microbiota and gut health, as they can be catalyzed and fermented by certain gut microbes and produce beneficial metabolites, such as short-chain fatty acids (SCFAs)[63]. In the gut, approximately 95% of SCFAs are acetate (C2), propionate (C3), and butyrate (C4)[64]. Studies have shown that acetate is mainly produced by bacteria, such as *A. muciniphila*, *Bifidobacterium* spp., *Bacteroides* spp., *Lactobacillus* spp., *Prevotella* spp., *Ruminococcus* spp. and *Streptococcus* spp. through the acetyl-coenzyme A pathway[65,66]. Propionate is mainly produced by *Bacteroides* spp., *Coprococcus catus*, *Dialister* spp., *Megasphaera elsdenii*, *Phascolarctobacterium succinatutens*, *Roseburia inulinivorans*, *Ruminococcus obeum*, *Salmonella* spp. and *Veillonella* spp. through three known pathways, *i.e.*, succinate pathway, acrylate pathway, and propanediol pathway[66,67]. Butyrate is produced primarily in *Anaerostipes caccae*, *Clostridium leptum*, *Coprococcus catus*, *Coprococcus eutactus*, *Eubacterium*

hallii, *Eubacterium rectale*, *Faecalibacterium prausnitzii*, and *Roseburia* spp., by enzymatic catalysis, such as butyryl-CoA dehydrogenase, butyryl-CoA transferase, and phosphotransbutyrylase or butyrate kinase[66,68]. SCFAs are critical modulators in pathophysiological events of diabetes. They act directly as histone deacetylase inhibitors and increase protective glucagon-like peptide-1 secretion[69], which decreases blood glucose levels, improves insulin resistance, and suppresses inflammation. Our previous studies have shown that dietary lipid adsorbent montmorillonite regulates intestinal absorption and gut microbiota, such as increasing SCFAs-producing *Blautia* bacteria, thereby preventing obesity and insulin resistance in HFD-fed murine models [70,71]. However, dietary effects on the shift of gut microbiota appear to be temporary [72]. Habitual diets, which have a longer lasting influence on the gut microbiome, may be a viable strategy.

Antidiabetic medications

Metformin is an oral antidiabetic medication. It has been used in the treatment of T2D for > 60 years due to its distinct effects on decreasing glucose production and increasing insulin sensitivity, as well as its safety profile. Metformin originates from *Galega officinalis*, a natural source of galegine[73]. Traditionally, activation of the AMP-activated protein kinase signaling pathway in the liver is thought to be the mechanism of its antidiabetic effects[74]. Recent findings indicate that metformin also orchestrates gut microbiome in mice and humans[43]. Sun *et al*[33] reported that metformin improves hyperglycemia through the gut microbiota-bile acid-intestinal farnesoid X receptor (FXR) axis in T2D patients. FXR is an important target in regulating glucose and lipid homeostasis. Metformin reduces the level of *Bacteroides fragilis* in the gut, leading to an increase in the FXR antagonist, glycoursodeoxycholic acid. Treatment with metformin also increased the abundance of probiotics *A. muciniphila* and SCFA-producing microbiota, such as *Butyrivibrio*, *B. bifidum*, and *Megasphaera* in murine and human studies[31]. Here, we summarize the role of the gut microbiome in the antidiabetic effects of metformin (Figure 2).

Acarbose, an α-glucosidase inhibitor, is an oral prescription medication used to control blood glucose in T2D treatment. Acarbose has been reported to alter the composition of gut microbiota in patients with T2D, in particular increasing the abundance of *Bifidobacterium longum* and decreasing the level of lipopolysaccharides [75]. Vildagliptin, a dipeptidyl peptidase 4 inhibitor, is an oral antihyperglycemic agent that enhances insulin secretion and suppresses glucagon release. Vildagliptin supplementation decreases the level of *Oscillibacter* and increases the proportion of *Lactobacillus* in HFD-induced mouse models[76]. Sitagliptin, another DPP-4 inhibitor, appears to exhibit antidiabetic functions during pregnancy in rats by reducing *Lactobacillus* spp. and increasing *Bifidobacterium* spp.[9,77]. Dapagliflozin, a sodium-glucose cotransporter-2 inhibitor, is a medication used to treat T2D. Treatment with dapagliflozin decreases the ratio of Firmicutes to Bacteroidetes and the abundance of *Oscillospira*, and increases the abundance of *A. muciniphila* in diabetic murine models [78,79]. Thiazolidinediones (TZDs) are a class of oral hypoglycemic agents for the treatment of T2D[80,81]. TZDs function through the activation of the peroxisome proliferator-activated receptor (PPAR) signaling pathway[82,83]. Pioglitazone, a member of TZDs, is widely used to treat T2D. It has been reported that treatment with pioglitazone reduces the α-diversity of the gut microbiota in murine T2D models, which may be one of the mechanisms mediating its antidiabetic function[79]. In our previous studies, Danshensu Bingpian Zhi, a synthetic derivative of danshensu and borneol, is a PPARγ agonist that prevents HFD-induced atherosclerosis, obesity, and insulin resistance in mice in part by reversing intestinal microbiota dysbiosis, such as increasing the ratio of Bacteroidetes to Firmicutes, increasing the level of *Akkermansia*, and reducing the level of the harmful bacterium *Helicobacter marmotae*[84]. These results suggest that gut microbiome is a potential target of many anti-diabetic medications clinically.

Traditional Chinese medicines (TCMs) have a long history of treating diabetes, but their mechanisms are not fully understood. Several studies have suggested that TCMs have multiple therapeutic effects on diabetes, including antioxidation, suppression of inflammation, protection of intestinal mucosal barrier, and inhibition of lipotoxicity, mainly by remodeling the gut microbiota[85]. Berberine, a well-known bioactive alkaloid extracted from TCM *Coptis chinensis*, has been used for the treatment of diarrhea and diabetes. Berberine is useful in diabetes management because its administration is associated with a decrease of obesity indices, such as body mass index and waist circumference[86]. Berberine maintains gut health in rats and humans with diabetes by increasing the abundance of *Bifidobacterium* and *Lactobacillus*, and decreasing the abundance of *Escherichia coli*[87,88]. Gegen Qinlian Decoction can

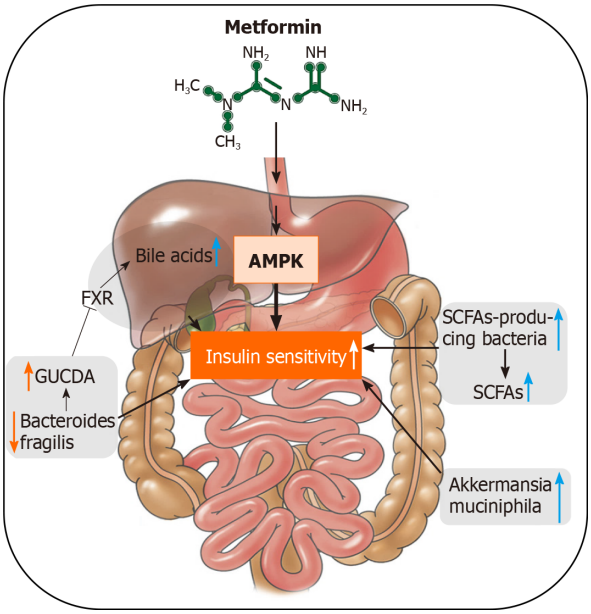

Figure 2 The schematic mechanisms of metformin act through the gut microbiome and the related beneficial effects on diabetes. AMPK: AMP-activated protein kinase; FXR: farnesoid X receptor; GUDCA: glycoursodeoxycholic acid; SCFAs: short-chain fatty acids.

relieve T2D in clinical trials, which is associated with an increase in the level of beneficial bacteria, such as *Faecalibacterium* spp.[89]. In addition, Banxia Xiexin Decoction, Huanglian Jiedu Decoction, and Qijian mixture also have beneficial effects by regulating gut microbiota[85,90,91]. These results suggest that gut microbiota is likely a new direction in elucidating the antidiabetic mechanism of TCMs.

CONCLUSION

Diabetes has become an urgent public health threat, and the growing trend of diabetes cases is expected to continue for the next two decades and beyond. Gut microbiome plays a critical role in health maintenance, and the dysregulation of gut microbiome can contribute to the development and progression of the disease. Here, we summarized the interaction between diabetes and the gut microbiota. Gut dysbiosis is increasingly recognized as a mechanism that induces metabolic diseases. Accumulating studies have shown that the gut microbiome is a key factor in the pathophysiology of diabetes, but research in this area is still in the early stages. Most of the studies have only shown that changes in the composition of the gut microbiota are associated with the progression of metabolic diseases. The exact causal relationship between a specific intestinal bacterium and phenotypic exposure is still not well understood. Further experiments using fecal or bacterial transplantation in germ-free mice and clinical studies are required to obtain a deeper understanding of the roles of individual bacteria in metabolic diseases. The use of metabolomics and transcriptomics to study the gut microbiome is a more effective strategy to understand the role of microbiota in the progression of host disease.

Traditionally, most pharmacological agents used for treatment of diabetes directly regulate the signaling pathways involved in glucose and insulin homeostasis. However, the gut microbiota is becoming an emerging therapeutic target for diabetes. In view of the good performance of herbal agents, particularly TCMs, in regulating gut microbiota, more consideration should be given to the use of medicinal herbs for the treatment of diabetes.

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