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REVIEW

Gut microbiota and diabetes: From correlation to causality and mechanism

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Abstract

In this review, we summarize the recent microbiome studies related to diabetes disease and discuss the key findings that show the early emerging potential causal roles for diabetes. On a global scale, diabetes causes a significant negative impact to the health status of human populations. This review covers type 1 diabetes and type 2 diabetes. We examine promising studies which lead to a better understanding of the potential mechanism of microbiota in diabetes diseases. It appears that the human oral and gut microbiota are deeply interdigitated with diabetes. It is that simple. Recent studies of the human microbiome are capturing the attention of scientists and healthcare practitioners worldwide by focusing on the interplay of gut microbiome and diabetes. These studies focus on the role and the potential impact of intestinal microflora in diabetes. We paint a clear picture of how strongly microbes are linked and associated, both positively and negatively, with the fundamental and essential parts of diabetes in humans. The microflora seems to have an endless capacity to impact and transform diabetes. We conclude that there is clear and growing evidence of a close relationship between the microbiota and diabetes and this is worthy of future investments and research efforts.

Key words: Diabetes; Microbiota; Causality; Mechanism; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Inflammation; Metabolites

Core tip: Current research continues to uncover associations between microbiota and diabetes [type 1 diabetes (T1D) and type 2 diabetes (T2D)], and these appear to involve metabolic effects and immune response processes. Understanding the consequences of balance in human gut microbiota and diabetes may prove very useful in developing future therapeutic interventions. This review summarizes recent studies in both mouse models and human cases that support a potential cause-effect relationship, and discusses the role of gut microbial metabolites on T1D and T2D.

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INTRODUCTION

Recently, studies of the human microbiome are capturing the attention of scientists and healthcare practitioners worldwide by focusing on the interplay of gut microbiome and diabetes. Understanding the consequences of balance in human gut microbiota and diabetes should prove very useful in developing future promising therapeutic interventions. Diabetes is a common chronic endocrine and metabolic disease, which impacts humans globally. Type 1 diabetes (T1D) is prevalent among children and adolescents, although the disease can occur at any age. The pathogenesis of T1D occurs when the endocrine system cannot produce insulin due to an autoimmune-mediated response leading to both inflammation and destruction of pancreatic β-islet cells. Type 2 diabetes (T2D) is a more prevalent form of diabetes most commonly occurring among adults and is usually caused by a combination of insulin resistance and an insulin deficiency.

Among the risk factors associated with diabetes are often things like a family history

of diabetes, unhealthy eating habits, and obesity. The increasing prevalence of diabetes is a worldwide phenomenon following the continuous growth in urbanization, changes in diet, and the emergence of more sedentary lifestyles. According to a 2019 report, about 463 million adults worldwide currently have diabetes and future projections indicate the number of diabetic patients will reach 700 million by 2045[1]. According to epidemiological observations, specific changes in the diversity of intestinal microflora are one of the characteristics of diabetic patients[2]. At the same time, there is also growing evidence of a close association between gut microbiota and diabetes[3].

The human gut is a complex ecosystem consisting of microbiome, host cells and nutrients[4]. There are about 100 trillion bacteria in the intestinal tract and they form the gut microbiota. Gut microbiota are composed of many diverse species of bacteria. These are taxonomically classified by genus, family, order and phylum. The intestinal microflora of healthy adults principally consists of six phyla: Firmicutes, Proteobacteria, Bacteroidetes, Actinobacteria, Fusobacteria and Verrucomicrobia. Bacteroidetes and Firmicutes occupy the dominant position in the human intestinal tract and play a pivotal role in the nutritional absorption system and support intestinal barrier enhancement. Genomic analysis of lean mice and healthy humans also confirmed the dominance of Firmicutes and Bacteroidetes, and most research indicates that Bacteroidetes outnumber Firmicutes[5].

Current research continues to find associations between microbiota and diabetes (T1D and T2D), and these appear to involve many metabolic effects and immune response processes, and most of these associate with more specific mechanisms. Some of the future research activities exploring gut microbiota balance variations and diabetes will lead to new interventional experiments, and potential evaluation of a causal hypothesis. This review provides an overview of studies that focuses on gut microbiota balance in humans with diabetes. So far, we know there is a range of recent evidence leading to some support for the potential causal role of gut microbiota in aspects of diabetic disease. It is now clear that future research will examine the potential for and discovery of the microbiota-related underlying mechanisms of diabetes[5,6]. It is only a matter of time and effort to follow the increasing evidence supporting these linkages.

DIET IS A CRUCIAL REGULATOR OF INTESTINAL MICROFLORA

The composition of the microbial community ecosystem is dynamic and its composition is dependent upon many factors[7]. Recent experiments using animal models indicate that intestinal microflora is regulated by factors including genes, medication, and diet. The gut microflora is easily altered by dietary changes. Experiments have shown that dietary changes can induce temporary shifts in a large number of microorganisms as rapidly as within 24 h[8]. Since diet is the main source of energy for individuals and a crucial method for humans to maintain health and growth, the diet composition has a big impact on gut microbiota[9]. It therefore follows that diet is also a vital regulator of gut microbiota. Gut microbiota composition also varies with an individual's age, and studies have shown these age-related gut microflora changes could possibly occur due to changes in diet at different ages and changes in inflammation due to some age-related diseases and changes leading to decreased immune system function[10]. At the same time, the varying composition of gut microorganisms has been identified in disparate geographical regions and this may also be related to different regional eating habits[11]. The gut microflora plays a pivotal role in the body's metabolism and immunity responses can also become a regulator of the effect of diet on the host's metabolic state[12]. On the other hand, these factors may also provide a potential impact on the onset of metabolic diseases like diabetes. The type, quality, components and source of human food intake will affect the composition of gut microbiome, as well as the functions and interactions in the microbiome ecosystem.

The main energy source of the gut microflora is dietary carbohydrates. The incidence of T2D is inversely associated with the total amount of dietary fiber intake. Dietary fiber is also found to impact intestinal microflora populations, and research indicates that fiber intake is associated with an increase in microbial diversity and the ratio of Firmicutes/Bacteroidetes[13]. Some studies have confirmed that an increase in dietary fiber intake also increases the abundance of the human intestinal microflora and leads to higher microflora richness. Fiber intake is also associated with higher microflora stability[14]. Dietary fiber intake promotes the fermentation of intestinal

microbes and this appears to cause an increase in short-chain fatty acids (SCFAs). As ligands of free fatty acid receptor 2 (FFAR2) and free fatty acid receptor 3 (FFAR3), SCFAs participate in the regulation mechanism of glucose homeostasis[15]. Propionic acid is reported to be produced mainly by threonine[16]; glycine, glutamic acid, lysine, ornithine and aspartic acid can be used to synthesize acetate; threonine, glutamic acid and lysine acid can be used to synthesize butyric acid, of which threonine can produce three main SCFAs[17]. Studies have reported that soluble fiber has a direct blood glucose lowering effect. Intake of soluble dietary fiber increases the viscosity of gastric juices, the more viscous fiber leads to gastric emptying times that are longer. Additionally these changes lead to small intestine transit time slowing, and increased starch digestion, which is associated with a reduced rate of glucose absorption, leading to changes in blood glucose and cholesterol concentrations[18]. Consuming more dietary fiber appears to reduce the risk of T2D, and is also associated with maintaining a healthy weight. Healthy adults and children can increase their intake of plant foods rich in fiber, while reducing total energy intake that is more often associated with high-sugar, high-fat, and low-fiber foods[19]. Nevertheless, some SCFAs appear to be involved in some of the mechanisms associated with diabetes, which also establishes the link between microbiota and diabetes[17,20].

A recent study combined measurements of intestinal microbiome diversity with diet history, and blood test parameters from volunteers. These data were evaluated using machine learning algorithms to predict how an individual's postprandial blood glucose production responded to real-life diets[21]. This study indicated that a personalized diet can successfully improve postprandial blood glucose elevation[21]. By combining these techniques and big data analysis, and the use of more specific medicinal nutrition recommendations shows the possible prevention and management of T2D with more effective personalized nutrition guidance. The widespread use of personalized nutrition also faces many challenges, such as the historic lack of reliable and repeatable results, also there are omics technology problems such as high cost, and the need for more research evidence to support actual effectiveness[22].

In addition to SCFAs, intestinal microflora appears to regulate lipopolysaccharide (LPS) levels and these levels are also thought to be involved in the development of diabetes[23]. Patients with T2D have fewer butyrate-producing bacteria than non-diabetic patients. Additionally, the ratio of Firmicutes/Bacteroidetes is also significantly lower in T2D patients than in non-diabetic patients[24]. By reviewing the results from across numerous studies, we can observe which intestinal microflora types and balances are co-occurring and possibly correlated with diabetes. In T2D patients, there is an abundance of *Bacteroides*, *Faecalibacterium*, *Akkermansia*, and there are lower concentrations of *Roseburia*, while *Ruminococcus* and *Fusobacterium* are elevated. Gut microbiota was also reported to have a relationship with T1D in previous studies[25]. Gut microbial communities appear to have an impact starting in infancy, and it is speculated that T1D is possibly related to the early effects of the gut microbiome. The interaction between the human body and the intestinal microflora appears to start at birth, and the development of the gut microbiome then evolves and goes through three fundamental stages: The first is a developmental stage (occurring during months 3-14), the second is a transition stage (occurring during months 15-30) and finally the third stage is a stable period (occurring during months 31-46)[26]. Abnormal gut microbiota is often observed in pre-diabetic patients. A controlled study was conducted to analyze 134 Danish patients with prediabetes. When these subjects were compared with normal controls, the intestinal microflora of patients with prediabetes showed abnormal characteristics, with low concentrations of *Clostridium* and mucin-degrading *Akkermansia muciniphila*[27]. In another study, vertical stool samples from 903 children aged 3-46 mo were analyzed, and the study found that early intestinal microorganism ecology is impacted by breastfeeding and childbirth[26]. The full implications of these observations, although not conclusive, appear to indicate that there is a developmental impact on microbiome development and the strength and outcome of these factors will need to be more fully explored in future research.

STUDIES USING ANIMAL MODELS

The mouse model is commonly used in the study of intestinal microflora, and the function of the intestinal microflora can model that for mammals. Studies using mice as models provide important insights and help to build an understanding of the relationship between the intestinal microflora and diabetes. Mice are generally used as the preferred model for research, because the intestinal structures of mice and human

subjects are quite similar. These models can also provide an evaluation of experiments designed to disturb the intestinal microbiota using controlled experimental apparatus. Closer observations of the microbiota composition is helpful in identifying and evaluating the potential causal relationships and possible mechanism of the interaction between host and intestinal microorganisms[28]. Although there is more work to be accomplished here, it is expected that a better understanding of how these balances in microbiota impact both health and diabetic disease processes will be forthcoming.

It is important to note that previous research indicated that when mice do not have gut microbiota (germ-free mice) they also have lower body fat and insulin resistance than conventional mice, and the tolerance of insulin and glucose in germ-free mice was higher than that observed in routinely fed mice. This study also paved the way for the examination of many potential mechanisms in the past decade[29]. This was followed by a subsequent intestinal microflora transplantation experiment, and the germ-free mice that received transplanted gut microflora from ob/ob mice showed a significant increase in obesity with associated insulin resistance[30]. In subsequent weight-loss surgery experiments, the correlation between obesity and intestinal microflora was also demonstrated, with an observed increase in fat mass in germ-free mice transplanted with altered microbiome[31].

In a recent study, the Koch hypothesis was a useful method to examine the possible causal link between gut microflora and obesity[32]. These studies all started to substantiate the potential cause-and-effect relationship. However, the results of gut microbiological studies in mouse models cannot be simply directly translated into human comparisons and these pitfalls of direct comparisons need to be avoided until more evidence from human studies can be completed to evaluate any potential causality.

TRANSLATIONAL STUDIES AND EXPLORATIONS

Studies in mouse models support the hypothesis of potential causality between gut microbiota and the development of obesity and diabetes, but so far there has been little research completed related to causality in human subjects. The reproducibility of human experimental studies is also sometimes limited, which may also be influenced by variations in differences among study settings, geographic locations of sample preparation, as well as inconsistencies in data analysis. Moreover, there are some studies which have produced contradictory observations and data in human research. It is unclear, as to the root cause of this variation; however, it may be partially attributed to different dietary habits and environmental/cultural factors around the world as well as to different experimental methods used. However, future conclusions regarding human microflora connections to diabetes will require intervention studies to determine if there is a causal relationship with microflora as a driving factor for disease development. To date, fecal microbiota transplantation (FMT), antibiotic therapy, diet, and probiotic therapy are considered effective in various intervention studies[33].

Contemporary research shows that FMT has also been considered an effective tool to gain evidence of microbiome association and the causality of many diseases[34]. In a randomized, double-blind controlled experiment of insulin-resistant men, patients received gut microbiota from lean body mass donors, and analysis of the experimental results demonstrated that FMT improved insulin sensitivity and the number of butyrate-producing bacteria also increased significantly. However, not all patients receiving FMT from lean donors experienced the same beneficial effects, and more research is required for comparative analysis[35].

Metformin

Forslund *et al*[36] proposed that changes in gut microbiome in diabetic patients are not entirely endogenous and can be explained in a large part by metformin treatment. Upregulation of glucagon-like peptide-1 (GLP-1) and peroxisome proliferator-activated receptors has been reported in healthy individuals and in T2D patients after metformin treatment. Metformin is also an insulin hormone regulator that has multiple effects in the intestine, such as increasing GLP-1 concentration in the intestine and extraction of glucose[37]. Metformin can reduce lipid absorption and inflammation caused by LPS, and can also reverse T2D-related changes because the abundance of several gut microbiota appears more similar to non-diabetic control levels when treated with metformin[36].

Recent studies have shown that metformin disrupts the microbial characteristics

associated with diabetes, including changes in the composition of the intestinal microflora[38]. A double-blind, placebo-controlled experiment of T2D patients showed that metformin altered the intestinal microflora balance in treatment-naive T2D patients, while germ-free mice had glucose tolerance after receiving metformin-modified microbiota and showed improved results[39]. Metformin was used in a controlled experiment in mice fed a high-fat diet (HFD), and the results showed that the abundance of the mucin-degrading bacteria *Akkermansia muciniphila* (*A. muciniphila*) was higher than that observed in the control group[40]. Similar conclusions have been found in other human studies[41]. A recent study analyzed the gut microbiome of Chinese T2D patients receiving different anti-diabetes drugs, and metformin recipients showed enrichment of *Turicibacter* and *Spirochaete*[42]. Another study used genomic analysis to analyze the composition of intestinal microflora in diabetic patients taking metformin. The results showed that *A. muciniphila* and several SCFAs-producing microbiota were low when compared to non-diabetic patients who had a relatively high abundance, and this study revealed some of the mechanism by which metformin changes the composition of intestinal microflora by enriching *A. muciniphila* and several SCFAs-producing microbiota[41].

Probiotics and intervention experiments

Probiotics appear to have a wide range of effects on the host, including improved regulation of insulin sensitivity, which may also be related to host metabolism mediated by the gut microbiome balance, by improving host metabolism composition, by reducing pro-inflammatory cytokines, and by reducing intestinal permeability[43]. In addition, probiotics have the potential to directly improve host metabolism and increase SCFAs production. Supplementing probiotics can also improve intestinal balance through the production of antibacterial compounds and competition with pathogens. Probiotics may also regulate the host's immune response, and activate specific gene activation and impact extra-intestine processes and disorders[44].

Numerous experiments in mouse models and human experiments have confirmed that multiple probiotics reduce insulin resistance by affecting gut microbiota and consequently, may influence health. Preliminary studies have shown that ingestion of fermented dairy products such as yogurt can transport lactic acid bacteria to the gut, alter gut microbial composition, inhibit the production of LPS, and increase the close connection of gut epithelial cells[45]. At the same time, a prospective, double-blind, randomized trial of 21 people with high glucose tolerance showed that oral administration of *Lactobacillus reuteri* also improved insulin secretion[46].

Recently, *A. muciniphila* has been frequently mentioned in current studies, and these studies show it reduces insulin resistance and reduces destruction of the intestinal barrier. *A. muciniphila* was reported to be less abundant in pre-diabetic patients, as well as among newly diagnosed T2D patients, suggesting that the low levels of *A. muciniphila* may be a biomarker for impaired glucose tolerance[47]. A recent study found that *A. muciniphila*-derived extracellular vesicles (AmEVs) can regulate gut permeability. The analysis of fecal samples revealed that AmEVs levels were low in T2D patients. Moreover, in a study of diabetic mice, the administration of AmEVs was associated with an observed decrease in fat content and an increase in glucose tolerance in diabetic mice[48]. Studies in mouse models have shown that supplementation with *A. muciniphila* can reduce low-grade inflammatory responses and metabolic disorders[49]. In another study of HFD mice, *Akkermansia* was reported to be associated with reduced LPS levels, which may be related to the ability of *Akkermansia* to maintain mucus layer thickness, which reduces intestinal permeability and LPS leakage[50]. *A. muciniphila* is a mucus-degrading bacterium, and its abundance is negatively correlated with glucose tolerance and fat accumulation in mouse models, but more evidence needs to be acquired in human studies to establish clear results[51]. The mechanism of decreasing insulin sensitivity of *A. muciniphila* may also be related to its membrane protein. Amuc_1100 is a special membrane protein isolated from *A. muciniphila*. Studies have shown that the special protein binds to Toll-like receptor 2 (TLR2) and participates in the protective mechanism of the intestinal barrier[52].

Clinical experiments are increasing in frequency and new results are encouraging. A recent randomized, double-blind placebo trial of 40 insulin-resistant adults who were orally supplemented with *A. muciniphila* showed that it played a role in reducing biomarkers associated with inflammatory responses, these biomarkers have also been linked to diabetes. Experiments have also shown that *A. muciniphila* improves insulin sensitivity in patients[53].

However, the regulatory effects of probiotics on improving insulin sensitivity have population limitations and may not work for everyone. It is worth noting, for example, that two recent studies have shown that probiotics have no effect on gestational

diabetes as this disorder appears entirely hormonal[54,55].

METABOLIC PRODUCTS AFFECT THE UNDERLYING MECHANISMS

Obesity and T2D are often characterized by changes in intestinal microflora, inflammation, and disruption of the intestinal barrier. Chronic, low-grade inflammatory response is a common characteristic of T2D and obesity, and this systemic inflammatory response is also thought to drive insulin resistance. Previous research in mouse models has confirmed that the intestinal microflora is responsible for the increased inflammatory response in obese patients[28]. Furthermore, the gut microbiome can interact with dietary components and habits to influence host insulin sensitivity, intestinal permeability, glucose and fat metabolism[56]. The gut microbiota has long been regarded as a virtual organ of human metabolic activity[57], and its metabolic activity interacts with insulin resistance and diabetes. Gut microbial metabolites can affect host physiological functions. Metagenomic analysis showed that the intestinal microflora of T2D patients and healthy individuals is often markedly different, and the decline in butyrate-producing bacteria may be the cause of impaired glucose metabolism[58]. Modification of gut microbiota caused by external interventions such as diet leads to dysregulation and secretory changes of intestinal microbial metabolites, triggering a variety of potential mechanisms leading to insulin resistance and diabetes. At the same time, intestinal microflora can also affect metabolism and the potential risk of diabetes by changing the way they respond to dietary ingredients[12]. There are many ways to interact with the host and intestinal microorganisms, and in the past decade, many studies were conducted to understand mechanisms for the analysis and hypothesis of microflora involved in regulating insulin resistance, including LPS and SCFAs. Most of the studies have focused on triggering the markers of diabetes: A low-grade inflammatory response and an immune response, in which intestinal microflora and its metabolites play a key role[5].

LPS

LPS is reported to induce inflammatory cytokines through immune cells and adipocytes, causing low-grade inflammation, while acetic acid or butyrate can regulate the function of immune cells. According to Gram staining analysis, the two most common phyla in clinical classification belong to different groups, namely Gram-positive bacteria and Gram-negative bacteria. LPS is derived from the cell wall of Gram-negative bacteria[59]. The LPS of gut microbiota binds to Toll-like receptor 4 (TLR4), then it initiates a signal cascade with good characteristics, inducing the inflammatory response and the expression and secretion of cytokines[60]. The TLR4 signaling pathway is considered to be one of the main triggers of the obesity-induced inflammatory response. Studies have shown that saturated fatty acids can cause insulin resistance and low-grade inflammation by activating the TLR4 signaling pathway[61]. At the same time, different studies have shown that TLR2 is also involved in the inflammatory response when the signaling cascade caused by LPS-LBP-TLR4 is activated[15]. The integrity of the gut barrier seems to play a crucial role in the development of obesity and T2D. The intestinal epithelium acts as a barrier, and its basic function is to limit the interaction between the intestinal microflora, the basic local immunity and other parts of the body[62]. The integrity of the gut barrier can maintain the functional balance of the mucosa, which can be maximally absorbed while maintaining an effective defense response[63]. Increased production of LPS by the intestinal microflora will also activate the endocannabinoid system. In addition, too much LPS may destroy the integrity of the intestinal barrier, and increase LPS absorption[64]. Animal studies have indicated that LPS is involved in the regulation of diabetes-related mechanisms, which can be characterized by the occurrence of increased inflammatory response[65].

SCFAs

SCFAs are composed of acetic acid, propionic acid and butyric acid. The deficiency in SCFAs is thought to be associated with T2D. Currently, studies have shown there is confirmation that SCFAs have a protective effect on the gut barrier, and result in a decrease in the number of butyrate-producing bacteria that may lead to changes in intestinal permeability. Studies have shown that butyrate can promote the expression of tight junction proteins and affect the mucosal barrier function[66], while acetate has also been reported to have a good performance in reducing mucosal permeability and enhancing the intestinal barrier function[67]. The SCFAs mechanism involves activation

of G proteins of the L-cells to promote the release of GLP-1 and peptide YY (PYY) to regulate glucose homeostasis, and at the same time, the SCFAs also effect the intestinal barrier, up-regulate 5'-AMP activated in muscle and liver tissues and the protein kinase signaling pathway, which are related to insulin resistance and inflammation, and oxidative stress may have a potential role[43].

Clinical studies have shown that dietary fiber promotes SCFAs production by gut microorganisms, while most other potential producers are relatively reduced in T2D patients[68]. In a recent study, intestinal microflora before and after dietary fiber interventions in volunteers were transplanted into germ-free mice. The study indicated the strong and significant association between gut microbiome and improved fiber glucose-induced host glycemic control. At the same time, the study proposed that when the SCFAs-producing bacteria promoted by dietary fiber have greater abundance and diversity, participants' glycated hemoglobin levels were improved[68]. On the other hand, SCFAs activate the vagal afferent neurons, which establish a connection between the intestinal information and the brain. This connection has been proved to play a role in controlling human feeding behavior, which also raises new considerations for the potential mechanism of SCFAs in increasing the risk of diabetes by controlling human feeding behavior and selection of dietary response[69].

In a recent study, genome-wide genotyping, intestinal genomic sequences, and fecal SCFAs level information from 952 normal blood glucose individuals were synthesized. A two-way Mendelian randomization (MR) analysis was used to assess causality, and the results showed that butyrate and propionate were proved to be involved in a causal relationship with diabetes, with oral glucose tolerance test showing a positive correlation between butyrate and improved insulin resistance and between malabsorption of propionic acid and the incidence of T2D, which offers evidence for the causal effect of gut microbiota on metabolic characteristics[70].

Butyrate

In a fecal bacteria transplantation experiment, insulin resistance patients received fecal microflora from insulin-sensitive donors, which resulted in a significant improvement in insulin sensitivity with increased abundance of butyrate-producing bacteria[71]. Through the analysis of human fecal samples, *Faecalibacterium prausnitzii* (*F. prausnitzii*) was found to be the main butyrate-producing bacteria. The abundance of *F. prausnitzii* and *Roseburia* in intestinal microflora of T2D patients is lower than that of healthy individuals, according to large scale metagenomic association studies in different populations[72]. Other studies have also demonstrated that the enrichment of *F. prausnitzii* can reduce inflammatory symptoms and insulin resistance. *Roseburia spp*. is also a butyrate-producing bacteria, which has a pivotal part in maintaining intestinal health and immune defense. It can regulate the dynamic balance of T cells by producing butyric acid[73]. Butyrate has a protective effect on the intestinal barrier by inducing the synthesis of mucin, it reduces the intestinal permeability and prevents bacteria from passing through. Butyrate also acts on the colonic epithelium, reducing oxidative stress and inflammation. In addition, the abundance of butyrate-producing bacteria is lower in prediabetic patients than in healthy people[27], which may indicate that the absence of butyrate-producing bacteria is one of the precursors of diabetes.

Bile acids and branched-chain amino acids

Bile acids are synthesized in the liver, and are transformed into secondary bile acids through the enzyme metabolism of gut microbiota[74]. In an experiment on rats, the intestinal microflora of oral bile acid treated rats was analyzed and showed there were significant changes in phylum levels and an increased ratio of Firmicutes/Bacteroidetes[75]. Secondary bile acids are associated with the regulation of insulin sensitivity through activation of Farnesoid X receptor (FXR) and the Takeda G protein-coupled receptor 5 (TGR5) receptors[76]. A study reported reduced genetic and diet-induced insulin resistance in FXR knockout mice[77]. FXR activation induces increased secretion of fibroblast growth factor 19 (FGF19 in humans, FGF15 in rodents), which improves glucose tolerance and insulin resistance[78]. Activation of the TGR receptor stimulates intestinal L cells to secrete GLP-1, thereby improving insulin sensitivity[79].

Branched-chain amino acids (BCAA) are thought to be related to the risk of developing T2D and are considered to be predictive markers for T2D[80,81]. Several studies have reported decreasing plasma BCAA levels in T2D patients[82,83].

A large cohort study also demonstrated the strong association between BCAA and diabetes, as well as the potential role of amino acid metabolism in the early stage of diabetes[80]. Studies in rats have demonstrated that high-fat dietary supplementation with BCAA also leads to insulin resistance[84]. Human studies have confirmed the

conclusion that supplementing BCAA in diet increases the risk of T2D and insulin resistance[85]. In a recent study, patients with T2D received a short-term dietary supplement of BCAA, which showed reduced insulin secretion after a meal and changes in the composition of the intestinal microflora. The synthesis pathway of BCAA has been shown to be related to *Prevotella copri* (*P. copri*) and *Bacteroides vulgatus* in intestinal microflora[86]. Subsequent experiments showed increased BCAA levels and increased insulin resistance in germ-free mice transplanted with *P. copri*[86]. The mechanism of BCAA inducing insulin resistance has been proposed to be attributed to the increased oxidation of free fatty acids and the activation of phosphatidylinositol 3-kinase (PI3K)[87]. However, the exact mechanism is still unclear and needs further study.

GUT MICROBIOTA AND T1D

Both T1D and T2D are associated with complex immune system and gut microbiome interactions. Gut microbiota disorders are associated with the pathogenesis of T1D, and the incidence of T1D is related to the interaction of gut microbiota and the innate immunity. Non-obese diabetic (NOD) mice have developed into the prototype model of T1D. The occurrence of T1D in NOD mice depends on the composition of gut microflora and LPS-mediated gut signals involving TLR4 and MyD88[88]. MyD88 is a key signal transduction factor in interleukin (IL)-1 and TLR signal transduction pathway. Its defect alters the composition of distal intestinal microflora. Studies have reported that NOD mice lacking MyD88 protein will not develop T1D[89]. In the follow-up study, the gut microflora of MyD88-deficient NOD mice protected by diabetes was transferred to wild-type NOD female mice, which reduced the intensity of pancreatitis and significantly delayed the occurrence of autoimmune glycosuria[90].

The gut microflora of preclinical T1D patients is characterized by the dominance of Bacteroidetes, the lack of butyric acid-producing bacteria, and the decrease of bacterial and functional diversity. A study in which colonic bacteria released large amounts of acetic acid or butyrate by feeding NOD mice with specific foods found that the key characteristics of the disease were negatively correlated with the concentrations of butyrate and acetate in blood and feces[91]. The mechanism is believed to be that the acetate diet reduces the frequency of autoimmune T cells in lymphoid tissues, while butyrate diet increases the number and function of regulatory T cells[91]. Human studies have also shown that SCFAs are involved in the prevention mechanism of early-onset human T1D. A recent prospective study demonstrated the protective effect of SCFAs on early-onset human T1D. This study analyzed 10913 metagenomes from 783 stool samples, and increased several bacterial pathways that promote SCFAs biosynthesis was found in healthy controls[92].

However, unlike T2D, transfer of the whole microbiota may not reduce the incidence of T1D. Recently, a study investigated the incidence of T1D in two NOD groups with different gut microbiota. Afterwards, 16S rRNA gene sequencing was used to analyze the gut microbiota with high or low incidence of T1D in the two groups of NOD mice, and the high incidence population was colonized with the microflora of the low incidence population. The results showed that the gut microbiota changed but the incidence of diabetes did not[88]. In another study, germ-free mice received fecal microflora from children with loss of β-cells, the result of which indicated that loss of β-cells after human T1D onset cannot be converted in germ-free NOD mice by FMT[93]. However, it is interesting that single symbiotic bacteria, such as *A. muciniphila*, can be used as probiotics to reduce the incidence of diabetes[88]. LPS also participates in the regulation of autoimmunity, most of which are *Escherichia coli* LPS involved in suppressing innate immune signals, but *Bacteroides dorei* LPS does not show significant improvement in T1D incidence[94]. In a recent study, intraperitoneal injection of *Escherichia coli* LPS in T1D mice showed a decrease in the incidence of T1D and an improved autoimmune response[94], while another study of NOD mice that received oral injection of *Escherichia coli* LPS also demonstrated an improvement in local immunity[95]. The concept that the pathogenesis of T1D is affected by gut microbiota has been well established in mouse models, but human studies on the microbiome in T1D are still few and far between to provide convincing evidence.

Gut microbial colonization in fetuses and infants can lead to dynamic changes in diversity, which may further affect disease susceptibility. A study of 33 infants with T1D genetic predisposition observed a significant decrease in alpha diversity among T1D progenitors, along with peaks in inflammatory organisms, gene function, serum and fecal metabolites, and this diversity difference occurred after serum conversion

and was determined to be specific to T1D[96].

The pre-clinical T1D patients' intestinal microflora is characterized by a dominant Bacteroidetes, with low stability and diversity of intestinal microflora. Studies have shown that these changes were found after the body produced auto-antibodies, which could indicate the role of gut microbiota in the autoimmune process, while the triggering mechanism of T1D disease was not determined[97]. There is growing evidence that islet autoimmunity is the first stage of T1D. Islet autoimmunity refers to the continuous existence of islet antigen autoantibodies, which usually begin in early childhood[98]. The role of gut microbiota in activating T1D is still a very vague concept, current studies have few observations or evidence to support the explanation that gut microbiota activates T1D, and most studies focus on the involvement of gut microbiota in the β-cell autoimmunity process. The causal relationship between intestinal microflora and T1D is still unclear, because most studies are only observational studies, and lack specific mechanical and intervention.

ORAL MICROBIOTA: ANOTHER FACTOR OF GUT MICROBIOME AND DIABETES

As the starting point of the digestive tract, the importance of oral microbiota and its association with the intestinal microbiota are received increasing attention. The oral cavity serves as an endogenous reservoir for gut microbial strains, and oral-fecal transmission is an important process that shapes the gastrointestinal microbiome in both health and disease[99]. Oral bacteria can translocate to the gut and lead to changes in its microbiota and possibly immune defense. It has been recognized that oral microorganisms may cause diseases mainly by a synergistic or cooperative way, and oral diseases (*e.g.*, caries, periodontal disease) and T2D appear to be mutually correlated[100]. Studies have reported significant differences in oral microbiota between patients with T2D and non-diabetic patients. Oral microbial biomarkers have been identified for T2D screening, diagnosis and prognosis[101-103]. Recently, researchers provided a possible mechanism for the improved understanding of how diabetes increases the risk and severity of tooth loss. Diabetes may cause changes in oral bacterial composition, and the oral microbiota of diabetic mice was found to be more pathogenic in studies transplanting to germ-free mice[104]. These studies suggested that oral microbiota is an important factor in the development of diabetes, and on the other hand, oral microbiota is also an important avenue for diabetes to cause other oral or systemic complications. This new area of investigation may represent another pathway for the oral-gut axis to potentially cause an increase in diabetic disease and deserves more in-depth research moving forward.

CONCLUSION

The current research into gut microbiome in the field of diabetes has gradually moved step by step from the initial correlation studies, which proved a strong association, to exploring the causality and potential mechanisms (Figure 1). It is very clear that as science looks to the future this will be a very promising frontier. It can be foreseen that the gut microbiota will be used not only as a biomarker for diabetes, but also as a target for potential therapeutic treatments. Through the intervention of gut microflora, it will eventually be possible to achieve a more precise and personalized diagnosis as well as treatment of diabetes (Table 1). This is only going to be possible with a significant investment in extensive multicenter, longitudinal, interventional and double-blind randomized clinical trials. Additionally, these will yield an extensive knowledge base upon which data science and exploration can occur. The scientific research community must proceed with a sense of urgency, if these data are to be used to their fullest advantage, as many new discoveries are waiting just ahead.

Table 1 A summary of products of gut microbiota and their mechanism of action

Gut microbiota products		Source	Mechanism	Function		Ref.
LPS		The cell wall of Gram-negative bacteria	Activates the receptor TLR4	Increase the occurrence of inflammatory response		[59,60]
SCFAs	Acetate	Carbohydrate fermentation	Activates the receptor FFAR2	Reduce the frequency of autoimmune T cells in lymphoid tissues	FFAR2 and FFAR3 stimulate the release of GLP-1 and PYY, which improve insulin secretion.	[15,91, 105]
	Propionate		Activates the receptor FFAR2 and FFAR3	Promote intestinal gluconeogenesis		
	Butyrate		Activates the receptor FFAR3	Increase the number and function of regulatory T cells		
Bile acids		The microbiota from host cholesterol	Bind to the receptor TGR5 and FXR	Improve insulin sensitivity		[74,76]
BCAA		*Prevotella copri* and *Bacteroides vulgatus*	Activate PI3K and increase the oxidation of free fatty acids	Increase the risk of insulin resistance		[86,87]

LPS: Lipopolysaccharide; TLR4: Toll-like receptor 4; SCFAs: Short-chain fatty acids; FFAR 2: Free fatty acid receptor 2; FFAR 3: Free fatty acid receptor 3; GLP-1: Glucagon-like peptide-1; PYY: Peptide YY; TGR5: Takeda G protein-coupled receptor 5; FXR: Farnesoid X receptor; BCAA: Branched-Chain Amino Acids; PI3K: Phosphatidylinositol 3-kinase.

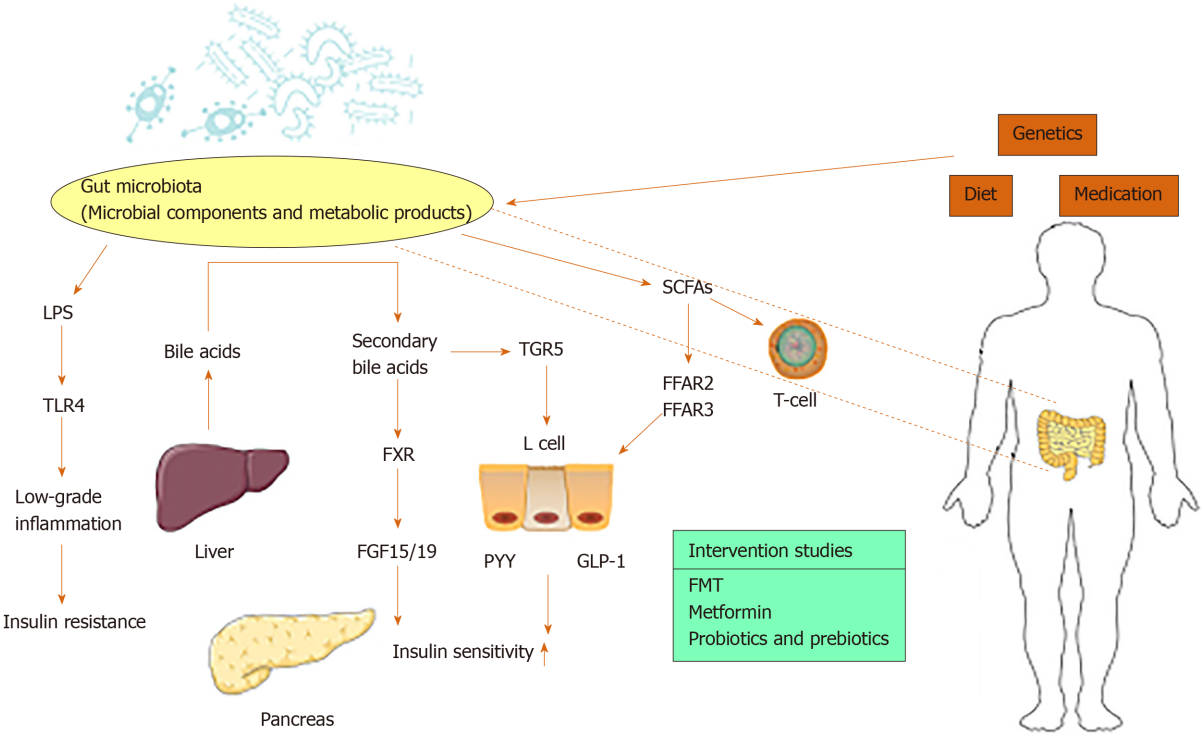

Figure 1 The main mechanism of gut microbiota affecting insulin resistance and diabetes. Gut microbes are influenced by diet, genetics and medication, and common types of interventions in humans include fecal microbiota transplantation, metformin and probiotics. Lipopolysaccharide (LPS), short-chain fatty acids (SCFAs) and bile acids are major regulators of diabetes. LPS binds to the Toll-like receptor 4 to induce low-grade inflammation and insulin resistance. Bile acids are synthesized by the liver and transformed into secondary bile acids through the metabolism of gut microbiota. Secondary bile acids activate Farnesoid X receptor to induce increased secretion of fibroblast growth factor 15/19. Secondary bile acids activate Takeda G protein-coupled receptor to stimulate intestinal L cells to secrete glucagon-like peptide-1 (GLP-1). SCFAs activate L cells to promote the release of GLP-1 and peptide YY to increase insulin sensitivity. SCFAs also have a regulatory effect on T cells. LPS: Lipopolysaccharide; TLR4: Toll-like receptor 4; FXR: Farnesoid X receptor; FGF15/19: Fibroblast growth factor 15/19; TGR5: Takeda G protein-coupled receptor 5; PYY: Peptide YY; GLP-1: Glucagon-like peptide-1; SCFAs: Short-chain fatty acids; FFAR 2: Free fatty acid receptor 2; FFAR 3: Free fatty acid receptor 3; FMT: Fecal microbiota transplantation.

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