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Microbiota associated with type 2 diabetes and its related complications

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Abstract

Recently, it has been established that the human resident microbiota plays key roles in health maintenance. Therefore, it has become an emerging prevention and treatment target for metabolic syndrome. The resident microbiota associated with chronic inflammation has been shown to contribute to the onset of type 2 diabetes mellitus (T2DM). Moreover, the microbiota is altered in the development of T2DM and its comorbid medical conditions/diseases, including diabetic retinopathy, kidney toxicity, atherosclerosis, hypertension, diabetic foot ulcers, cycstic fibrosis and Alzheimer's disease. Besides, some anti-T2DM regimens are also based microbiota metabolism-dependent mechanism. This review summarizes the current knowledge concerning the altered microbiota in the pathogenesis of T2DM and its related complications, which provides novel insights into these diseases and the potential intervention strategies from the microbiology point of view.

Keywords: Microbiota; Type 2 diabetes; T2DM complications

1. Introduction

The rapid increase of cases of type 2 diabetes mellitus (T2DM) in the past decades has made it a widespread metabolic disorder. In recent years, an increasing understanding of how our microflora is linked to obesity-related T2DM has provided a new potential target for reducing the risk of T2DM. The human body reservoir harbors trillions of bacteria and the genetic content of the gut microbiome is 150 times more than that of other parts of the human body [1]. However, the host–microbe interactions have not been fully elucidated. The aim of this review is to expand our view on key roles of microflora during the onset and development of T2DM as well as its complications.

1.1. Gut microbiota in the pathogensis of type 2 diabetes

It is well established that the gut microbiota is involved in the process of energy harvest accounting for the development of obesity [2]. Some researches support the view that the gut microbiota is essential for the host immunity development [3]. As one of the most concerned obesity-related disorders, T2DM is associated with abnormal energy metabolism and low-level chronic inflammation in fat tissues [4,5]. Some hypotheses have proposed its relation with the presence of gut microbiota.

Principally, the gut microbiota plays an important role in the progression of prediabetes conditions, such as insulin resistance. Growing evidence in clinical studies suggested that obese people with insulin resistance were characterized by an altered composition of gut microbiota, particularly an elevated *Firmicutes*/*Bacteroidetes* ratio compared with healthy people [6,7]. Furthermore, transplantation of the obese gut microbiota in animals greatly affected the energy harvest of hosts [7]. Consequently, it is proposed that altered microbiota in obesity modulates intestinal permeability and increases metabolic endotoxin secretion that lead to chronic low-level inflammation, the pathogensis of insulin resistance and onset of T2DM. [8,9]. Recently, commensal bacterial species, such as *Bacteroidetes thetaiotaomicron*, *Akkermansia muciniphila* and *Escherichia coli*, were showed to have different influence on the intestinal mucus and glycocalyx layer, which may affect intestinal permeability [10]. Besides, microbiota-dependent changes in gut tight-junction proteins, endocannabinoid system and

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intestinal alkaline phosphatase activity may be also involved in altered intestinal permeability and the pathogensis of insulin resistance [9].

Moreover, the vicious circle between altered microbiota and the triggered low-level inflammation has also been considered as a deterioration factor in the development of T2DM. Accumulating evidence has revealed that T2DM patients exhibited an altered intestinal microbiota which was characterized by a decrease of *Bacteroidetes*/*Firmicutes* ratio and some functional bacteria (e.g. *Bifidobacteria*) with an increase of various opportunistic pathogens and some endotoxins-producing Gram-negative bacteria [11–13]. Firstly, *Bacteroidetes/Firmicutes* alteration may modify the host energy metabolism through a specific polysaccharide utilization loci mechanism [14]. Moreover, the accumulation of gut-derived bacterial inflammatory molecules (e.g. LPS, peptidoglycans and flagellin) in intestine is thought to accelerate the inflammation in T2DM [15,16]. Besides, gastric bypass surgery, an effective way to normalize the blood glucose level to treat T2DM, could reduce body weight due to the alteration of the microbiome at the distal gut [17].

It has been confirmed that some probiotic strains are able to modulate blood glucose homeostasis, and hence improve T2DM [18]. Several mechanisms have been proposed. Firstly, probiotic could acted as an effective immune system modulator against altered-microbiota induced chronic inflammation. It is well-established that obesity induced chronic low-level inflammation is a leading cause of the progression of T2D [19,20,21]. Some probiotics have been confirmed to prevent onset of diabetes through down-regulating inflammatory IFN-γ and IL-2 or IL-1β or enhancing anti-inflammatory IL-10 production in diabetic animal studies [22–24]. Recently, *Lactobacillus reuteri* GMNL-263 have been demonstrated to suppress serum glucose, insulin, leptin, C-peptide, glycated hemoglobin, GLP-1 level, inflammatory IL-6 and TNF-α in adipose tissues and PPAR-γ and GLUT4 gene expression in high fructose-fed rats [25]. Furthermore, human studies have revealed that probiotic yoghurt consumption could reduce hs-CRP level and improve HOMA-IR score in pregnancy which is also considered as metabolic syndrome [26,27]. In addition, some probiotic strains show favorable antioxidative effect which is one of the effects against chronic inflammation. They are apparently able to alleviate pancreatic oxidative stress which can lead to chronic inflammation and apoptosis of pancreatic β-cells [28,29].

Moreover, the supplementation of certain probiotic strains can potentially modulate the lipid metabolism and result in the reduction of the serum total cholesterol level and LDL-cholesterol, which will reduce the risk of T2DM [30]. Besides, endotoxemia has been identified as a triggering factor of insulin resistance in mice, making the suppression of endotoxemia by probiotic another potential protective mechanism [9]. An oral administration of *Lactobacillus casei* Shirota, was able to enhance the expression of plasma lipopolysaccharide-binding protein (LBP) and consequently reduce endotoxemia in murine models of obesity and T2DM [31]. In another study, the consumption of the probiotic strain, *Bifidobacterium animalis* subsp. *lactis* 420, suppressed the bacterial translocation process from intestine to tissues, which might lead to metabolic bacteremia in the early onset of T2DM [32]. From the perspective of nutrition, a novel probiotic strain, *L. casei* Zhang, was recently proven to exhibit osteocalcin-elevating effect leading to improvement of oral glucose tolerance in impaired glucose tolerance (IGT) rats. This was probably achieved via gut *Bacteroides fragilis* enriched vitamin K2 mechanism [33].

2. Microbiota and T2DM complications

2.1. Diabetic retinopathy

Diabetic retinopathy accounts for more than 60% incidence in T2DM [34]. As expected, a higher frequency of Gram-positive bacteria and a higher proportion of coagulase negative staphylococci was detected in diabetic patients, especially those with retinopathy [35,36]. This result was supported by Bilen et al., who found that *Staphylococcus epidermidis* and *Staphylococcus aureus* were the predominant conjunctival organisms in T2DM patients, and the frequency of *S. aureus* isolated from the patients' eyes were higher than that of T1DM and healthy subjects [37]. Parkinson's disease is also one of complications with chronic diabetic neuropathy in T2DM [38]. Kusbeci et al. observed that the occurence of *S. aureus* was significantly higher in the conjunctival flora of Parkinson's patients than in healthy controls [39].

2.2. Renal toxicity and kidney stones

A high proportion of T2DM patients also suffer from clinical condition of chronic kidney toxicity, such as kidney stones. This is probably due to the disruption of colonic epithelial permeability which was implicated in the pathogenesis of T2DM and chronic kidney toxicity [40]. By phylogenetic microarray analysis, chronic kidney disease patients showed significant changes in 190 microbial operational taxonomic units (OTUs), particularly the high abundance of the *Enterobacteriaceae* compared to the healthy control group [40].

Moreover, Zheng et al. recently demonstrated that the bioconversion of melamine by gut microbiota, particularly Klebsiella, was essential for renal toxicity and the formation of crystal stones [41]. *Oxalobacter formigenes*, a commensal gut microbe, has been shown to improve the clinical condition of kidney stone patients [42]. However, commonly available probiotics, including *Lactobacillus* and *Bifidobacterium* species, were insufficient in degrading oxalate to treat kidney stones [43,44]. Besides, the extent of calcium oxalate stone formation may be dependent on the microbiota. This is evidenced by the low expression level of vitamin K epoxide reductase complex subunit 1 (VKORC1) in patients with calcium oxalate urolithiasis. The expression of VKORC1 could be influenced by vitamin K2 producing gut bacteria [45,46].

2.3. Hypertension

Hypertension and T2DM are closely related to each other in clinical setting. Apart from being a complication to T2DM, it is also a major risk factor for cardiovascular disease and a

symptom of metabolic syndrome. Recent evidence suggests that metabolic syndrome is partially regulated by the gut microbiota [6]. However, only very little is known about the role of the host gut microbiota in the case of hypertension. One experimental finding supporting the hypothesis of blood pressure regulation by the gut microbiota was provided by Pluznick et al. using a mouse model. Propionate is one of the end-products derived from the gut microbiota. It was revealed that, in response to propionate, the expression of renal olfactory receptor 78 (Olfr78) was increased, in turn mediating the secretion of rennin [47]. Consequently, the blood pressure was elevated. On the contrary, G protein-coupled receptor (GPR41), a short-chain fatty acid receptor, negatively regulated the blood pressure. Hence, it was concluded that these gut microbiota-derived short-chain fatty acids, in particular propionate, participated in the blood pressure regulation process via both receptors.

Furthermore, it has been reported that *Lactobacillus johnsonii* La1 ingestion could not only maintained low blood glucose level in streptozotocin (STZ)-induced diabetic rats, but also prevent rats from elevated blood pressure by reducing the renal sympathetic nerve activity and enhancing the parasympathetic nerve activity through the sympathoadrenal axis [48,49].

2.4. Atherosclerosis

Most T2DM patients tend to have higher levels of serum lipids, which predisposes them to atherosclerosis. Associations between microbiota and atherosclerosis have been proposed. Koren et al. analyzed the oral, gut and atherosclerotic plaque microbiota in atherosclerotic patients [50]. Good correlation was found between total abundances of *Veillonella* and *Streptococcus* in the oral cavity and the atherosclerotic plaque. Moreover, several oral and intestinal bacterial taxa, including *Streptococcus*, *Neisseria* and *Fusobacterium*, are correlated with the plasma cholesterol levels.

It is well established that probiotics with bile salt hydrolase activity could accelerate the bioconversion of cholesterol to primary bile, showing acids a serum lipids-reducing effect [30]. Moroti et al. reported that the administration of a synbiotic beverage called shake, which contained *Lactobacillus acidophilus*, *Bifidobacterium bifidum* and oligofructose, markedly increased the plasma HDL cholesterol and decreased the condition of fasting glycemia in elderly T2DM patients [51].

2.5. Cystic fibrosis

Patients with cystic fibrosis (CF) are also associated with high incidence of T2DM [52]. There is increasing evidence that an altered microbiota in CF respiratory tract plays an important role in its pathogenesis. The most commonly isolated bacterial species in airways of CF patients were *Haemophilus influenzae*, *S. aureus*, *Pseudomonas aeruginosa* and *Burkholderia cepacia* complex species [53]. Nowadays, high-throughput sequencing methods, such as 16S amplicon pyrosequencing, were applied to evaluate the whole composition of the airway microbiota. Goddard et al. found that CF lungs were typically dominated by only one to three species by direct sampling of explanted lungs [54]. They also observed that the microflora in the sputum and throat specimens could not represent the typical CF microflora.

A recent study monitoring the development of gut and respiratory microbiomes in CF infancy revealed that both compartments shared some common core microbes and the temporal fluctuation of microbiota over time was in concordance with each other. Moreover, a change in diet resulted in the alteration in the airway microbiota composition [55]. These together suggest that diet, gut microflora and the development of the respiratory tract microbiota are linked with one another. Because of this link, it is logical to hypothesize that the oral administration of probiotics may reduce symptoms caused by CF. At least two individual studies confirmed the probiotic effects of *Lactobacillus* GG in alleviating the intestinal inflammation and pulmonary exacerbations rate in CF patients [56,57]. Another common symptom of CF children is the malabsorption of bile acids. Roy et al. showed that antibiotic treatment reversed this condition, which was due to the reduction of gut anaerobes and their related enzymatic activities, such as bile salt hydrolase (BSH) [58]. Gut bile salt hydrolases deconjugate glycine or taurine from bile salts. The deconjugated bile salts are more efficient in lipid emulsification and absorption in the gut. Hence, the application of BSH-bearing probiotics may be another potential treatment for CF patients.

2.6. Diabetic foot ulcers

Diabetic foot ulcers leading to infection and limb loss are both linked to an increasing risk of age-related diabetes. Several well-explored microorganisms, including *Staphylococcus* species, *P. aeruginosa* and *E. coli*, etc., were isolated from patients with infected diabetic foot ulcers [59]. The main plantar foot normal flora are coagulase-negative *Staphylococcus* species, which are recognized as strong competitors for the infection-associated *S. aureus*. Recently, Redel et al. found that the ratio of non-pathogenic *Staphylococcus* to pathogenic *S. aureus* on the feet of diabetic men was lower, compared to the normal subjects [60]. By bacterial 16S rRNA gene pyrosequencing, Gardner et al. analyzed the microbiomes in diabetic foot ulcers and revealed that the ulcer depth and duration were negatively correlated with the abundance of *Staphylococcus*, whereas the ulcer duration was positively correlated with that of *Proteobacteria* [61].

2.7. Alzheimer's disease

T2DM may result in an increase in risk in Alzheimer's disease (AD) and these may share common pathogenic mechanisms [62,63]. Vignini et al. summarized the recent experimental evidence and potential mechanisms that link the two medical conditions, including the possible roles of insulin deficiency or insulin resistance in facilitating cerebral β-amyloidogenesis, which accounts for the increased risk of diabetes patients to dementia [64]. In addition, AD had even been considered as the type 3 diabetes [65].

Currently, little data is available on the resident microflora of AD patients, thus how they are related to each other remains poorly understood. To date, only one study has directly compared the gut physiology and microbiota structure between wild type and AD transgenic mice. The gut alteration in AD transgenic mice was characterized by an increase of Gram-negative bacteria accompanied by mucosal disruption [66]. Moreover, the amyloid precursor protein (APP) expression level was significantly upregulated in the intestine of AD, but not in the control mice.

Even though the research area of the gut microbiota in AD is understudied, the possibility of preventing from or treating AD via enteria bacteria has been considered. Indole propionic acids (IPAs) are putative drugs for treating AD and T2DM [67,68]. The plasma amino acid metabolites, including the bioactive indole-containing metabolites, of germ-free mice were significantly affected as compared to the normal mice. Moreover, the bioconversion of indole to indole-3-propionic acid was found to be solely dependent on the gut microbiota [69]. Therefore, manipulations of gut microbiota seem to be a key to restore the plasma IPA level. Another metabolic characteristic of AD was the loss of GABA(A) receptors in the hippocampus of the brain [70]. The probiotic strain *L. rhamnosus* JB-1, an effective modulator of the gut microbiota, was proved to be able to increase GABA(Aα2) in the hippocampus of mice [71]. These are direct evidence showing the interaction between the residence flora and the host metabolism, which offers novel potential prophylaxis or treatment targets for AD.

3. Anti-T2D regimens concerning microbiota

In recent years, due to side-effects of anti-T2D drugs for glucose or insulin resistance control (e.g. metformin and pioglitazone) and anti-inflammatory drugs for T2D complications (e.g. NSAIDs), natural anti-T2D compounds extracted from plants potentially with less side effects have drawn more attention [4,72]. Particularly, these drugs with GI and cardiovascular side effects brought high risks for long-term use [73]. Berberine, a component from traditional Chinese herb *Coptis chinensis*, has been recently demonstrated to have anti-diabetic effect through modulating microbiota composition since it is mainly absorbed by gut [74]. The major bioactive constituents of Ginsing, another important anti-diabetic Chinese herb, were mainly from microbiota-mediated metabolism of ginsenosides [75]. Inhibition of intestinal α-glucosidase is another strategy to control the increase in blood glucose at early onset of T2D [76]. However, drugs for this target may lead to GI side effects [77]. A great deal of polyphenols, a series of natural compounds from tea, coffee, wine, fruit, vegetables, and chocolate, can inhibit glucose metabolism enzymes to exert anti-diabetic effect with no side effect [78,79]. Typically, wine polyphenols have been confirmed to significantly modulate some taxa of gut microbiota and reduce serum lipids and inflammatory C-reactive protein in humans [80]. Moreover, the microbiota is also important for the metabolism of polyphenols (e.g. catechin and gallocatechin from green tea) promoting their bioavailability in the small intestine [81].

4. Conclusion

In summary, great progress has been made in the field of the resident microbiota in T2DM in recent years. Microbiota contributes not only to low-level inflammation in the onset of T2D, but also to the further development of T2D through inflammatory components. It has also been extended to various T2DM related complications, including diabetic retinopathy, kidney toxicity, atherosclerosis, hypertension, diabetic foot ulcers, cycstic fibrosis and Alzheimer's disease. These studies together support the crucial role of microbiota in maintaining the intestinal barrier integrity, sustaining a normal metabolic homeostasis, protecting the host from infection by pathogens, enhancing host defense system and even influencing the nervous system in T2DM. Microbiota-mediated mechanism is also involved in some anti-T2D regimens using natural compounds from plants. However, the potential mechanisms linking the microbiota to T2DM have not been fully elucidated and continuing research efforts are needed.

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