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Review Article

Targeting gut microbiota: a potential promising therapy for diabetic kidney disease

Zhonge Chen[1*], Shuishan Zhu[2*], Gaosi Xu[3]

[1]Medical Center of The Graduate School, Nanchang University, Nanchang, China; Departments of [2]Gastroenterology, [3]Nephrology, Second Affiliated Hospital, Nanchang University, Nanchang, China. [*]Equal contributors.

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Abstract: Conventional studies reveal a contributory role of gut microbiota in the process of diabetes mellitus (DM) and end-stage renal disease (ESRD). However, the mechanism through which gut microbiota influence diabetic kidney disease (DKD) is ignored. In the present article, we reviewed the changes in gut microbiota of patients with DM, DKD as well as ESRD, and how this may contribute to the progression of DKD. Although further studies are needed to either selectively change the composition of the gut microbiota or to pharmacologically control the metabolites of microbiota, the gut microbiota represents a new potential therapeutic target for DKD.

Keywords: Gut microbiota, diabetic kidney disease, diabetes mellitus, end-stage renal disease

Introduction

The gut microbiome is a complicated ecosystem with a large number of microbiota---100 trillion, representing an approximated 5000 species and a high density of microbiota---10^{12} per gram of luminal contents, and roughly 1.5 kg of bacteria [1, 2]. The bacterial concentration augments from the stomach (10^2-10^4 cells/ml) to the colon (>10^{12} cells/ml) in keeping with the decreased oxygen tension [3]. The microbiota of the gut benefit the host by adjusting the development of the gut, hindering the growth of pathogen, practicing the immune system, fermenting unused energy matrix, and generating vitamins, such as biotin, cobalamin and vitamin K [4].

Dysbiosis refers to an unbalanced gut microbial community with alterations in the composition and metabolic activities of the gut microbiota. The interference of normal gut microbiota has been involved in the pathogenesis of a variety of diseases, such as type 1 diabetes (T1DM) [5], type 2 diabetes (T2DM) [6], diabetic kidney disease (DKD) [7], and end-stage renal disease (ESRD) [8]. In the present review, we described how specific changes in gut microbiota can affect host with these diseases, especially DKD, and how these findings may give rise to novel therapeutic targets for them.

Diabetes mellitus

The prevalence and incidence of both type 1 and type 2 diabetes are increasing all over the world. The acceleration of diabetes outdistances the speed of genetic variation, which eliminates genes as singular factors in the disease. Alterations in environmental conditions such as diet, hygiene, antibiotic utilization, and other medical practices were associated with the increase of diabetes [9]. Gastrointestinal tract and pancreas are anatomically connected by the enteroinsular axis, therefore, the signals derived from the gut have the potency to induce effects in the pancreas [10].

Type 1 diabetes mellitus

T1DM is a chronically immune-mediated illness and has remarkable character that is the selective decrease of insulin-producing-β cells in the pancreas of susceptible individuals, which inevitability lead to the perpetual requirement for exogenous insulin [11]. Although researches

Table 1. Alterations of gut microbiota in patients with T1DM

Models (children)	Alterations of gut microbiota	Mechanisms and its applications	References
4 with two autoimmune antibodies, and 4 controls	Butyrate-producing and mucin-degrading bacteria↓ Bacteria that produce SCFAs other than butyrate↑	In autoimmune subjects, non-butyrate-producing and lactate-utilizing bacteria prevent mucin synthesis to maintain gut integrity	[12]
18 with two diabetes-associated autoantibodies, and 18 controls	lactate and butyrate-producing species↓ Bifidobacterium adolescentis↓ Bifidobacterium pseudocatenul-atum↓ Bacteroides genus↑	Low abundance of bifidobacteria and butyrate-producing species adversely affect the intestinal epithelial barrier function and inflammation	[13]
4 developed autoimmune diseases or T1DM, and 4 controls	Bacteroides ovatus↑ Firmicutes↓	Children destined for autoimmunity have a less diverse and stable gut microbiota	[15]
29 converted to T1DM-related autoimmunity, 47 remained healthy	Bacteroides dorei and Bacteroi-des↑ Vulgatus↑	Early changes of gut microbiota are probably useful for predicting T1DM autoimmunity in genetically suscep-tible infants	[19]

T1DM: type 1 diabetes mellitus; SCFAs: short-chain fatty acids.

Table 2. Characteristics of some gut microbiota

Gut microbiota	Gram stain	Requirements	Characteristics
Bacteroidetes	Negative	Anaerobe	Help host to decompose polysaccharide and improve utilization rate of nutrients.
Firmicutes	Positive	Aerobe, anaerobe	Make intestinal tract absorb more heat from food and lead to obesity.
Clostridium leptum	Positive	Anaerobe	Degrade cellulose to produce butyric acid, supply energy for host and promote development of epithelial cells.
Bifidobacterium spp	Positive	Anaero	Inhibit growth of harmful bacteri, compound vitamin, produce organic acid, and stimulate intestinal peristalsis.
H. pylori	Negative	Anaero	Pathogenicity is associated with adhesion factor, urease, protease, cavitating toxin and cytotoxin.

about gut microbiota on the risk of developing T1DM are still in the primary stage, original studies manifested that the gut microbiota of individuals with prediabetes or DM are different from that of healthy people. The gut microbiota in individuals with preclinical T1DM has its special characteristics, e.g. a short of butyrate-producing bacteria, the Bacteroidetes dominating at the phylum level, decreased bacterial diversity and reduced community stability [5]. Furthermore, several researches have reported a lower microbial diversity among subjects with T1DM compared with healthy volunteers [12-14]. Therefore, alterations in the gut microbiota may contribute to disease progression in patients with increased risk of T1DM (**Table 1**).

In a case-control study in Finland, the gut microbiota of healthy children was different from those with autoimmune disorders [15], with the remarkable decrease of Firmicutes and increase of Bacteroidetes in the children destined for autoimmunity. Furthermore, the ratio of Firmicutes to Bacteroidetes may be a diagnostic indicator for autoimmune disorders---T1DM. Insulitis, characterized by autoimmune reactions resulting in T1DM, has been reported in non-obese diabetic (NOD) mice and been expedited under germ-free (GF) conditions, indicating an interaction between the immune system and the microbiota [16]. The immune system and the gut microbiota develop synergistically [17]. The β-cell autoimmunity was associated with the alterations of the specific commensal bacteria, including a decrease of Clostridium leptum in NOD mice and the abundance of Bacteroides species in individuals with later T1DM [18, 19]. A better understanding of the function of the specific bacteria and their effects on immune function may stand out methods that the modification of gut microbiota could lessen the autoimmune attack on β-cells [9].

Type 2 diabetes mellitus

T2DM is characterized by increased blood glucose, which is an outcome of a gradual defect of insulin secretion in the background of insulin resistance (IR). Frequently, individuals with T2DM present with vascular complications at the time of diagnosis. Similar to T1DM, increasing evidences indicate that the interaction between gut microbiota and host is probably one of the factors influencing the risk and development of T2DM. Researchers identified a decrease of Firmicutes and an enrichment of Betaproteobacteria in T2DM compared with non-diabetic subjects, which was positively correlated with serum glucose concentration of oral glucose tolerance test [20]. Therefore, the authors demonstrated that T2DM was correlated with the changes of composition of gut microbiota. Interestingly, Chinese T2DM patients exhibited a reduction of butyrate-producing bacteria, such as Eubacterium rectale, and Faecalibacterium prausnitzii as well as an increase of several opportunistic pathogens, e.g. Bacteroides caccae, and Clostridium hathewayi [6]. These related gut microbiota have different characteristics (**Table 2**).

Individuals with low bacterial richness, demonstrated by low gene copies (LGC) were compared to those with high bacterial richness, demonstrated by high gene copies (HGC). After evaluating the association among gene copies, obese phenotype and serum markers, the study found that LGC group was characterized by more marked overall adiposity, IR, dyslipidaemia and inflammatory phenotype, such as increased highly sensitive C-reactive protein and higher white blood cell counts than seen in HGC group [21]. HGC group presented an increased production of organic acids such as short-chain fatty acids (SCFAs), which was correlated with increased hydrogen production and methane production. These findings indicated that the LGC subjects with metabolic disturbances displayed the inflammation-associated microbiota and higher risks for prediabetes and T2DM [22].

The study showed that the enrichment of Akkermansia muciniphila, a mucin-degrading bacterium improved the metabolic profile of T2DM mice. Treatment with A. muciniphila reversed high-fat diet derived metabolic disorders including fat mass gain, metabolic endotoxemia, adipose tissue inflammation, and IR [23]. The increase of Akkermansia muciniphila induces Foxp3 regulatory T cells in visceral adipose tissues, elevates glucose tolerance, and enhances the antidiabetic effects of metformin, which suggest that pharmacological administration of the gut microbiota in favour of Akkermansia is probably a potential treatment for T2DM [24].

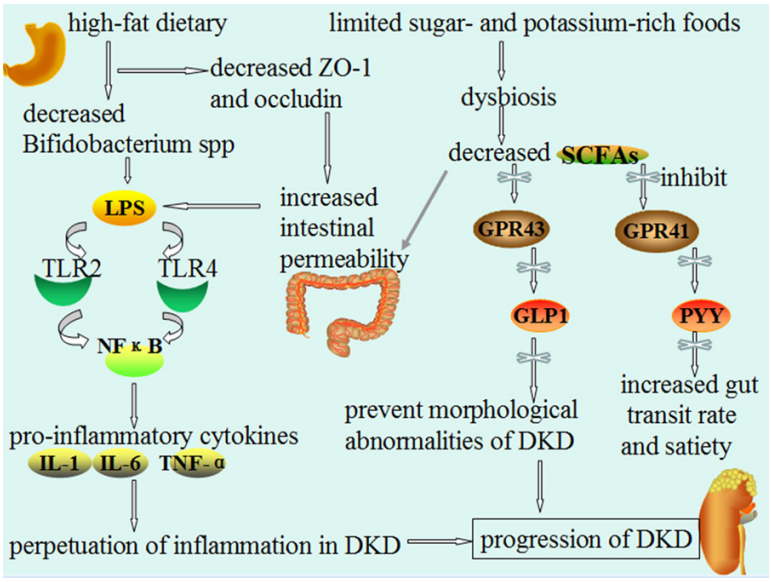

Figure 1. The gut microbiota plays critical roles in the lipid metabolism abnormalities and the progress of DKD. The decreased Bifidobacterium spp as well as the expressions of tight junction proteins zonula occludens-1 (ZO-1) and occludin due to high-fat diets are negatively correlated with high portal plasma concentration of lipopolysaccharide (LPS). LPS initiates inflammatory responses through Toll-like receptor TLR2/4-related pathways, by which LPS mediates the activation of nuclear transcription factor κB (NFκB) and leads to the secretion of pro-inflammatory cytokines tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1) and IL-6. Furthermore, DKD patients are limited with the consumption of sugar and potassium-rich foods, which can be fermented to short-chain fatty acids (SCFAs) and provide the major nutrients for the normal colonic bacteria. Their limited consumption increases the intestinal permeability and leads to a leakage of LPS into the portal blood circulation. The inflammatory responses as well as the decreased SCFAs play the central role in the progression of DKD. SCFAs can activate G protein coupled receptors GPR41 and GPR43 on the intestinal epithelial cells. Stimulation of GPR41 leads to the release of peptide YY (PYY) that can increase the gut transit rate and satiety. Activation of GPR43 alleviates inflammation and stimulates the release of glucagon like peptide 1 (GLP1), which could prevent the onset of the morphological abnormalities of DKD.

Diabetes is related to a set of relevant lipid metabolism abnormalities. The levels of triglyceride were elevated in adipose tissues and liver, while declined in serum of conventionalized mice compared with GF mice, indicating that gut microbiota play a critical role in lipid metabolism [28]. The increased plasma concentration of LPS is a trigger factor for the maintenance of the continuous inflammatory state in the host as response to high-fat diets. Furthermore, the expressions of tight junction proteins zonula occludens-1 (ZO-1) and occludin were significantly decreased [29]. The disruption of the intestinal barrier in obese mice increases the intestinal permeability and leads to a significant and continuous leakage of LPS into portal blood circulation, which increases the severity of metabolic endotoxemia and the concentrations of inflammatory cytokines [30, 31]. Furthermore, the decreased cecal contents of Bifidobacterium spp due to high-fat diets are negatively correlated with high portal plasma concentrations of LPS [32].

Diabetic kidney disease

DKD is the leading cause of ESKD and its increasing incidence has imposed heavy socioeconomic stress on healthcare systems all over the world. Although the metabolic disorder is historically considered as the pathogenesis of DKD, recent studies have established that the inflammatory responses also play a central role in the progression of DKD. The regulations of Toll-like receptor 2 (TLR2) and TLR4 have been involved in the pathogenesis of the perpetuation of inflammation in DKD [25]. Accumulating evidences indicate that the inflammatory responses initiated by lipopolysaccharide (LPS) in host are mediated by TLR2/4-related pathways [26, 27].

TLR2 can recognize the components of bacterial cell walls and lipid-containing molecules, mediate the activation of nuclear transcription factor κB (NFκB), and produce pro-inflammatory cytokines, which consequently transduce cellular inflammatory signals. The TLR4/cluster of differentiation-14 (CD14)/myeloid differentiation-2 pathway is triggered by LPS, which mediates the activation of NFκB and leads to the secretion of pro-inflammatory cytokines tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1) and IL-6. Mice without TLR2 show an increase of insulin sensitivity and a faster clearance of glucose by attenuating the expression of inflammatory cytokines. TLR4 gene silence with pharmacologic blockade inhibits the inflammation and IR initiated by LPS [28].

Currently, inhibitors of TLR2 and TLR4 are undergoing clinical trials in various inflammatory models of diseases.

Gut microbiota ferment the dietary polysaccharides to produce monosaccharides and SCFAs, acetate, propionate, and butyrate, which can be absorbed and contribute approximately to 5% to 10% human energy resources [33]. SCFAs can activate G protein coupled receptors GPR41 and GPR43 on intestinal epithelial cells. The stimulation of GPR41 leads to the release of peptide YY (PYY) that can increase the gut transit rate and satiety [34]. Activation of GPR43 alleviates inflammation and stimulates glucagon like peptide 1 (GLP1) release from L cells [35]. GLP1 act the antidiabetic effects by inhibiting food intake, stimulating insulin secretion, and inducing β-cell proliferation [36]. Incretin agonist of GLP1 receptor (GLP1R) improves pancreatic islet function, reduces blood pressure, dyslipidaemia and inflammation, and decreases body weight in T2DM. The incretin-based agent can not only inhibit the reabsorption of renal tubular sodium, also decrease glomerular pressure and albuminuria, then prevent the onset of morphological abnormalities in DKD [37]. DKD patients are limited with the consumption of sugar and potassium-rich foods, including fruits and vegetables, to avoid hyperglycemia and hyperkalemia. Because fruits and vegetables are the major sources of polysaccharides that can be fermented to SCFAs and provide the major nutrients for the normal colonic bacteria, their limited consumption profoundly affects the gut microbiota and the progression of the DKD. (**Figure 1**).

A meta-analysis indicated a relationship between H. pylori infection and the risk of DM and DKD [38]. The bacterium is able to play its pathogenic role in the whole disease process. Given the existing literature, there is a fundamental necessity to find out the relationship between DKD and gut microbiota.

End-stage renal disease

The major contributing factors to gut microbiota dysbiosis in subjects with ESRD consist of slow flow rate of colonic contents, limited consumption of indigestible complex carbohydrates [39], impaired protein assimilation [40], iron treatment [41], and frequent utilization of antibiotics [42]. Higher urea concentration of body fluids in patients with ESRD leads to an increasing influx into the gastrointestinal tract, in which it is converted to ammonia then to ammonium hydroxide by urease-possessing microbiota [43]. Protein can be fermented by gut microbiota and converted to different metabolites, including phenols and indoles. Analysis of the microbial genomics found the increase of bacteria which possess urease, uricase, and p-cresol- and indole-forming enzymes and the decrease of bacteria which possess SCFAs forming enzymes in ESRD [44].

ESRD patients always exhibit endotoxemia, the magnitude of which is connected with the severity of systemic inflammation [45]. The major contributing source of circulating endotoxin in ESRD is originally produced by the gastrointestinal tract. An autopsy study performed by Vaziri et al discovered that chronic inflammation was observed throughout the gastrointestinal tract of the patients receiving regular hemodialysis [46]. These inflammatory changes extended from esophagus to large bowel and sometimes coexisted with peptic ulcer disease or ischemic lesions. Existed studies demonstrated the role of ammonia and ammonium hydroxide produced via hydrolysis of urea by the urease-possessing bacteria in the disruption of intestinal barrier [47], which is compounded by the decreasing production of SCFAs due to limited consumption of potassium-rich foods. SCFAs generated from the fermentation of carbohydrates by the symbiotic bacteria are the major nutrients for colonic epithelial cells [48].

Recent advances in our understanding of the physiologic functions and pathologic consequences of dysbiosis have led to the exploration of reestablishing symbiosis, which includes therapies targeting the colonic microenvironment in ESRD aim to modulate gut microbiota, for example probiotic therapy with administration of live microbial species, prebiotics to restore symbiotic and suppress dysbiotic microbiota, a combination of prebiotics and probiotics, and targeting the adsorption of microbial-derived toxins [39].

Conclusion

The gut microbiota plays its pathogenic roles in the entire progression from DM to DKD, and the

subsequent ESRD. Previous studies focused mainly on the association between microbiota and DM or the relationship between microbiota and the ESRD. Unfortunately, they ignored the disease transitory stage---DKD. Future studies on the correlation between gut microbiota and may lead to the further understanding of the pathogenesis and discoveries of the treatment for DKD.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Gaosi Xu, Department of Nephrology, Second Affiliated Hospital, Nanchang University, No. 1, Minde Road, Nanchang 330006, China. Tel: +86(0)791 86270383; Fax: +86(0)791 86270383; E-mail: gaosixu@163.com

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