

## Efficacy of probiotics on the modulation of gut microbiota in the treatment of diabetic nephropathy

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### Abstract

Diabetic nephropathy (DN) is a major cause of end-stage renal disease, and therapeutic options for preventing its progression are insufficient. The number of patients with DN has been increasing in Asian countries because of westernization of dietary lifestyle, which may be associated with the following changes in gut microbiota. Alterations in the gut microbiota composition can lead to an imbalanced gastrointestinal environment that promotes abnormal production of metabolites and/or inflammatory status. Functional microenvironments of the gut could be changed in the different stages of DN. In particular, altered levels of short chain fatty acids, D-amino acids, and reactive oxygen species biosynthesis in the gut have been shown to be relevant to the pathogenesis of the DN. So far, evidence suggests that the gut microbiota may play a key role in determining networks in the development of DN. Interventions directing the gut microbiota deserve further investigation as a new protective therapy in DN. In this review, we discuss the potential roles of the gut microbiota and future perspectives in the protection and/or treatment of kidneys.

**Key Words:** Diabetic nephropathy; Short chain fatty acids; Superoxide dismutase; Reactive oxygen species; D-amino acids; Gut microbiota; Diabetes mellitus; Renal disease

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**Core tip:** Evolving evidence suggests that the gut microbiota may play a key role in the development of diabetic nephropathy (DN). Interventions aimed at the gut microbiota deserve further investigation as a novel protective therapy in DN. We review the potential roles of the gut microbiota in the protection of kidneys and in the development of DN.

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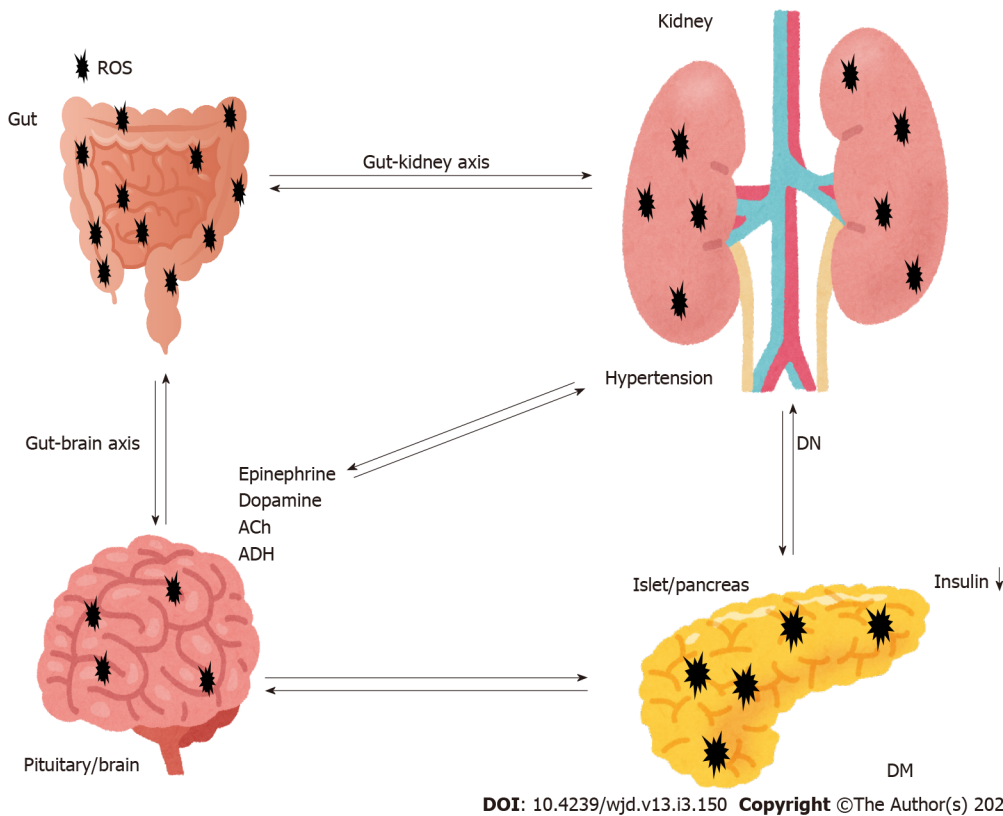
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## INTRODUCTION

Diabetic nephropathy (DN) is a chronic disorder occurring in nearly 40% of patients with diabetes[1]. DN is an important cause of end-stage renal disease and a micro-vascular complication of diabetes mellitus (DM)[2,3]. Some dietary factors might be involved in the increase in renal failure in association with DM, showing that the number of patients with DN and/or DM has been increasing in Asian countries because of westernization of dietary lifestyle[2,3]. Pathogenesis of DN may be multifactorial and complex. Early DN has no noticeable clinical symptoms, however, hyperglycemia may be a significant risk factor for DN and/or DM[4]. Sustained elevated blood glucose could lead to changes in the downstream transcription factors and/or gene expression in kidney glomerular cells[5]. Kidney fibrosis and albu-minuria are key pathological processes of the advanced stage of DN[6], but oxidative stress and/or inflammation may also be important mechanisms for the pathogenesis of DN[7]. In general, oxidative stress and inflammatory responses are almost not distinct, because one reaction would intensify the other pathogenesis. Both DM and chronic kidney disease (CKD) may have a common pathophysiological mechanism within a chronic inflammatory state and/or oxidative stresses [8]. Among them, high levels of reactive oxygen species (ROS) could induce inflammatory cytokines in the kidney[9], which might accelerate the development of DN. Inflammation of the kidneys can lead to proteinuria and/or persistent hypertension, which can proceed to renal failure. Hence, successful treatment of the microcirculation in patients with DN has become a superior strategy for the prevention of DN. This reasonable treatment should be discovered immediately. Recently, it has been shown that pathogenesis of DN is associated with certain gut microbiota[10]. The importance of probiotics is widely recognized in various diseases. Besides, studies have shown that crosstalk between host and microbiota might be relevant pathologically in patients with DN[11]. For example, alterations in the gut microbiota are associated with the development of proteinuria[12], and type 2 DM[13]. Changes to the gut microbiota have also been reported in DM and DN[14]. The gut microbiota might well communicate with the kidneys, and the collapse of this relationship might result in the development of renal dysfunction. Accordingly, the gut microbiota could be an important defense against the pathogenesis of kidney disease. Dietary lifestyles have radically changed over the last century in developed countries, and are characterized by reduced dietary fiber and/or increased high-fat consumption[15]. Hence, the changes could be linked to alteration of gut microbiota[16]. Abnormal intestinal metabolites and disruption of the intestinal barrier owing to the gut dysbiosis might facilitate harmful substances produced in the gut entering the circulatory system[17]. These situations allow us to hypothesize that dietary changes could lead to a microbiome that modifies positively the threshold and/or the speed of developing DN and/or DM.

## GUT-KIDNEY AXIS IN THE PATHOGENESIS OF DN

Although the significance of the gut microbiota has yet to be completely determined, it is obvious that an intricate symbiotic relationship might exist between host and microbe. In addition, the interaction has recently attracted interest in the study of the pathogenesis of various disorders. The human body holds numerous bacterial and/or microbial cells; the majority of which exist in the gut[18]. The microbiota is a complex community of more than 100 trillion cells in healthy human intestines[19]. The normal gut microbiota could protect the kidney, whereas gut dysbiosis of the microbiota could facilitate kidney disorders[20]. Furthermore, alterations in the microbiota are gradually being linked to the development of various other diseases such as inflammatory bowel disease, cancer, psychiatric disorder, and cardiovascular disease[21]. The gut-kidney axis could additionally affect metabolic and/or immune pathways in addition to the related diseases[22]. The gut-kidney axis is largely mediated by metabolites produced by the gut microbiota, which might regulate physiological function of several organs including the brain, pancreas, adrenal glands, kidneys, *etc.* (Figure 1). For example, components of the immune system might have a key role with cytokines in communication between the gut and kidneys [23]. Furthermore, crosstalk between the metabolic and immune pathways has a significant role in keeping a good balance in the kidneys[23]. Intestinal responses to inflammation and/or infections are intricate. If microbiota-immune pathways overstimulate tolerance to some inflammation, greater inflammation may accelerate progression of renal disease and/or its complications. Accordingly, gut dysbiosis has frequently been associated with progression of many kidney diseases[24]. In addition, accumulation of uremic toxins, which are derived from dietary metabolism in the gut and/or liver, has distinct effects



**Figure 1 Representation of the pivotal role of gut-kidney axis crosstalk with the brain and the pancreas in the pathogenesis of diabetic nephropathy.** Hypothetical image of the pathogenesis pathway for diabetic nephropathy (DN). Sympathetic activation is a common feature in disorders of the brain as well as gut and kidneys. The brain is responsible for sympathetic outflow contributing to an increase in blood pressure and pathogenesis of the gut and kidneys. Dysbiosis in the gut results in an imbalance of intestinal homeostasis. Pathological events in the brain, pancreas, adrenal glands, gut and kidneys significantly contribute to the development of hypertension and DN. Note that some critical pathways such as inflammation pathway have been omitted for clarity. Ach: Acetylcholine; ADH: Antidiuretic hormone; ROS: Reactive oxygen species; DM: Diabetes mellitus; DN: Diabetic nephropathy.

on the kidneys. For example, the increase in urea increases its influx into the bowel lumen from epithelial cells, where it is hydrolyzed by gut microbiota urease to ammonia[25]. Subsequently, ammonia byproducts may increase the bowel pH, leading to the severe mucosal damage[26]. Accumulation of the uremic toxins in combination with inflammation may also increase the risk of renal disease [27]. Therefore, key factors in kidney disease are function of the gut microbiota and/or the action of gut dysbiosis. Inflammatory bowel disease and DM are indeed multifactorial diseases, and both are chronic diseases associated with increased risk of various diseases including cardiovascular disease, which indicates that the gut is associated with host physiological functions[28]. Interestingly, the prevalence of inflammatory bowel disease in adults with type 1 DM is higher compared to that of nondiabetic controls [29]. It is plausible that the gut-kidney axis might be involved in the pathogenesis of inflammatory bowel disease and DM. Similarly, the gut microbiota may be involved in the damage of other organs, hence targeting the gut microbiota could represent a future therapeutic approach in various diseases. However, the potential impact of gastrointestinal-related disorders on the development and/or progression of DN remains to be elucidated.

## LEVELS OF SHORT-CHAIN FATTY ACIDS, ROS, AND D-AMINO ACIDS MAY BE INVOLVED IN THE DEVELOPMENT OF DN

Diabetic model mice fed with a high-fiber-diet are less likely to develop DN compared with diabetic control mice fed with a no-fiber diet[30]. High-fiber diet might decrease the expression of genes encoding inflammatory cytokines related to DN[30]. In general, fibers positively improve the dysbiosis of microbiota with promoting the production of short chain fatty acids (SCFAs) (including butyrate, acetate and propionate) in gut microbiota[31], which might also increase the production/release of cytokines and/or chemokines[32]. In addition, SCFAs are able to inhibit intestinal inflammation and/or oxidative stress[33]. Major SCFAs (acetate, propionate and butyrate) are derived through glycolysis of glucose to pyruvate or acetyl-CoA. The SCFAs regularly induce glucagon-like peptide 1 secretion through stimulation of a G-protein-coupled receptor (GPCR)[34]. Gut microbiota in older people may

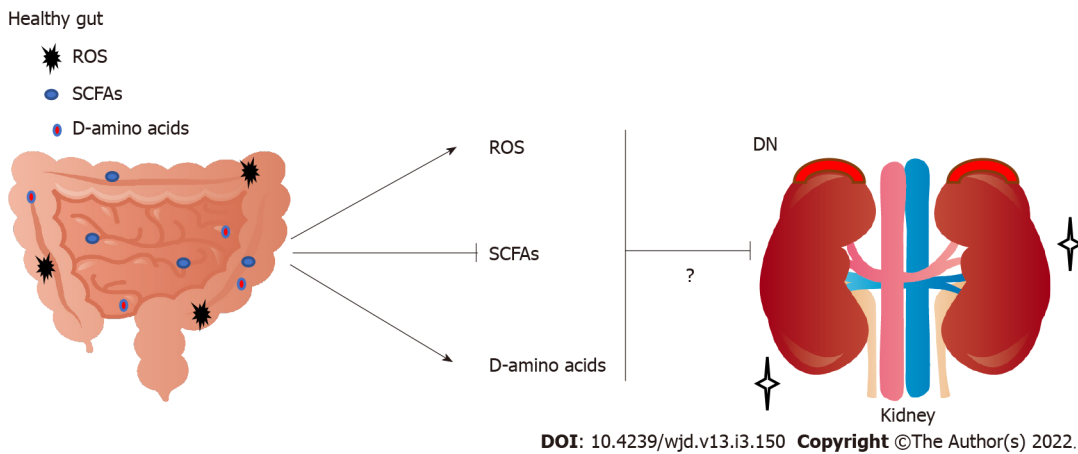
weaken SCFA production[35]. Those SCFAs have various effects on endocrine cells in gut *via* the GPCRs such as G-protein-coupled receptor (GPR)43 or GPR109A[36]. SCFA-treated diabetic mice have been shown to be protected from nephropathy, suggesting that SCFAs protect renal cells from injury by oxidative stress in DN[37]. It has been shown that butyrate, one of the SCFAs produced by gut microbiota, plays a protective role in DN, which contributes in various physiological processes predominantly by inhibiting histone deacetylases (HDACs)[38]. In addition, providing sodium butyrate has been shown to protect renal cells from oxidative damage and/or apoptosis in type 2 DN mice[39]. Consistently, sodium butyrate has inhibited high-glucose-induced apoptosis of tubular epithelial cells in normal kidneys[40]. Sodium butyrate also lowers plasma glucose and nuclear factor-B expression in the kidneys and attenuates kidney injury[41]. In experimental mice, suppression of HDACs by sodium butyrate may explain the decrease in apoptosis in the kidneys[42]. HDACs can regulate cell proliferation, migration and apoptosis, which are organized by a family of enzymes important for chromatin remodeling, keeping a dynamic balance with histone acetyltransferases in expression of several genes [43]. Valproate, an HDAC inhibitor, has also been shown to decrease renal injury and/or renal fibrosis [44].

The signaling pathways triggered by hyperglycemia appear to have a pivotal role in diabetic complications due to the production of ROS and/or additional oxidative stress, which finally leads to apoptotic cell death in various tissues[45]. ROS includes superoxide anions, hydroxyl free radicals, and hydrogen peroxide[46]. The mitochondrial electron transport chain is considered a major endogenous source of ROS[47]. Production of excess ROS leads to increased membrane permeability and serious cellular damage[48]. Such overproduction of ROS links to the pathological condition of altered metabolic pathways in the kidneys and disturbed renal function known as nephropathy[49]. Once ATP synthesis is dysregulated in this hyperglycemic situation, it can result in excess production of ROS, which leads to kidney failure[50]. Furthermore, high glucose exposure with excessive ROS can lead to renal podocyte apoptosis in experimental DN[51]. Antioxidants including ubiquinone (also termed coenzyme Q10), ascorbic acid, and resveratrol have been tested in animal models of kidney diseases with some evidence of therapeutic benefits[52]. Epidemiological studies have also found an association between high levels of ROS and risk of DN[53]. Therefore, downregulation of ROS and/or oxidative stress might have a crucial role in regulating diabetic complications. Besides, ROS have been revealed to function as second messengers in several signal transduction pathways[54,55].

Studies have shown the clinical significance of D-amino acids in several kidney diseases[56]. For example, the combination of blood level and urinary dynamics of D-serine effectively separates CKD from non-CKD[57]. D-amino acids in body fluids are also a promising early detection marker for kidney disease[58]. However, excess D-serine can cause kidney damage in rats[59]. In this case, it has been shown that D-serine administration can initiate extensive necrosis in renal proximal tubules[59]. In contrast, administration of D-alanine does not induce kidney injury[60]. Furthermore, protective effects of low-dose D-serine have likely been shown to suppress renal damage, which may promote the hypoxia-mediated proliferation of tubular epithelial cells[61]. In addition, D-cysteine administration can also protect the kidneys from ischemia-reperfusion injury, which might be useful to treat various renal diseases[62]. D-aspartate plays a role during development and neurogenesis[63]. D-aspartate treatment might produce favorable effects during demyelination and remyelination in the nervous system[64]. Furthermore, the ovary-inducing activity of D-tryptophan is more effective than that of L-tryptophan [65]. These data suggest that D-amino acids have both beneficial and harmful effects on tissue development and/or tissue-protection (Figure 2).

## GUT MICROBIOTA COULD CONTRIBUTE TO HEALTHY KIDNEYS

Carbohydrates are metabolized by gut bacteria into monosaccharides and oligosaccharides, and they could be fermented into SCFAs. As shown above, SCFAs are one of the primary end products of gut fermentation that have considerable effects on host physiology. SCFAs can act as signaling molecules between the gut microbiota and host, and may have a protective effect on the renal function of patients with CKD. In particular, butyrate improves the intestinal barrier and reduces lipopolysaccharide influx into the blood, which could attenuate progression of DN[66]. We provide here a perspective of gut-kidney axis applied in search of renal disease management associated with the gut microbiome, which may theoretically be beneficial for future treatment of DN. Diet is known to be an essential regulator of gut microbiomes[67]. Many studies have confirmed the association between nutrition and the human microbiome in maintaining human health, suggesting significant roles of bacterial metabolites in both health and disease[68]. Trillions of bacteria present in the intestinal and colon lumina constitute the human gut microbiota[69]. Dietary intake could control microbiota whose fermentation may produce various metabolites including SCFAs[70]. The metabolites might additionally regulate the growth of pathogens by competing for nutrients. For example, parenteral nutrition has been associated with a change in the microbiota, altering SCFA production, and inducing gut mucosal atrophy[71]. The SCFAs made by the healthy gut microbiota have anti-inflammatory properties, including proliferation of regulatory T cells[72,73]. In addition, a significant role for regulatory T cells has been revealed in type 2



**Figure 2 Implication of increased short-chain fatty acids, decreased reactive oxygen species, and increased D-amino acids derived from gut in the renal protection and/or exacerbation against the progression of diabetic nephropathy.** Arrowheads mean stimulation and/or progression, whereas hammerhead represents inhibition. Note that some critical pathways including hormonal regulation have been omitted for clarity. SCFAs: Short-chain fatty acids; ROS: Reactive oxygen species; DN: Diabetic nephropathy.

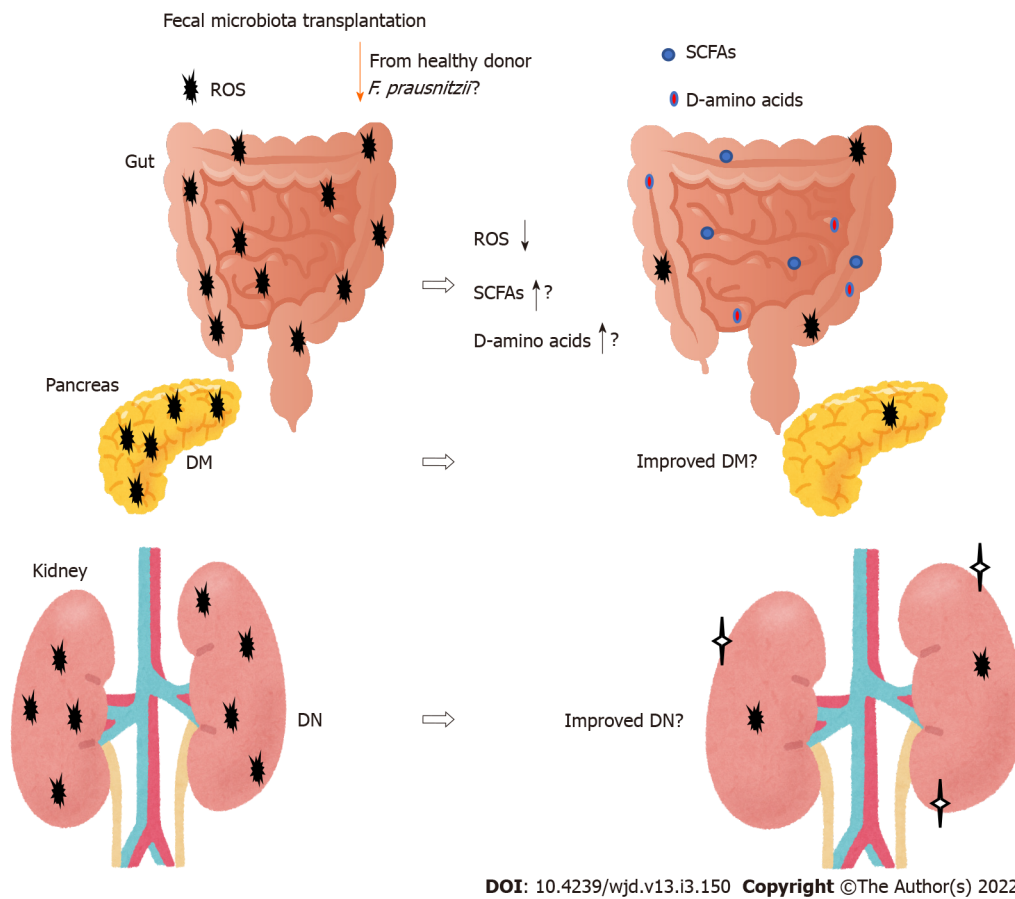
diabetes for protection against DN[74]. In addition, SCFAs have favorable effects on  $\beta$  cells, potentiating glucose-stimulated insulin release and/or maintaining  $\beta$ -cell mass through inhibiting apoptosis[75]. Furthermore, propionate, has been shown to prevent adipogenic differentiation of specific stem cells [76].

Many studies have emphasized the relationship between the gut microbiota and oxidative stress[77]. In general, ROS production has a defense mechanism that could elicit cytotoxicity against several pathogens then reduce the burden of infection[78]. Redox signaling is also found in response to microbial signals *via* the gut epithelial NADPH oxidase 1[79]. Therefore, microbial ROS might rigorously control signaling processes for appropriate immunity and/or the gut barrier[80]. Numerous bacterial species of the microbiota can reduce mitochondrial ROS production[81]. For example, microbial products can upregulate the activity of superoxide dismutase, which results in reduced ROS levels and then decreased cellular apoptosis[82]. In addition, microbial excess ROS might disturb other important pathways of host cells, suggesting that ROS-mediated signaling can regulate various cellular processes in order to keep the host healthy[83]. Epithelial cells may also exhibit increased ROS production in response to several harmful bacteria[84]. In the gut, epithelial appropriate ROS production in response to the gut bacteria may play a signaling role in the host[85]. It is likely that there are many ROS-sensitive important enzymes that could be affected by alterations in the gut redox conditions.

Finally, the gut microbiota have the largest genetic capacity to metabolize D-amino acids that are utilized as nutrients to support bacterial growth to regulate spore germination[86]. Therefore, one possible source of D-amino acids in mammals may be their gut microbiota. In general, many bacterial species encode racemases that convert L-amino acids to D-amino acids[87]. For example, D-alanine production is associated with a relative abundance of bacterial species with racemases such as those of *Enterococcus* and *Lactobacillus* in the gut microbiota[88]. Different bacterial species may produce distinct profiles of D-amino acids[89]. Higher D-amino acids levels have been related to the gut microbial mass [90]. Oral intake of a peptide containing specific D-amino acids may reverse the diabetes-associated pathological alterations in the kidneys[91] (Figure 2). Noteworthy differences in the microbiota composition have been discovered in patients with kidney disease compared with healthy controls[92]. Consequently, treatment options for DN should include dietary therapy affecting the gut microbiota. Therapeutic interventions would nevertheless represent a potential target of the microbiota for prevention and/or treatment of DN.

## CONCLUSION

New therapies for DN are emerging. One method that may affect the gut microbiota composition is fecal microbiota transplantation (FMT) (Figure 3). The beneficial effects of the transplantation are dependent on the host responses, however, which may provide a potential treatment strategy for type 2 diabetes[93]. In particular, transplantation of *Faecalibacterium prausnitzii* (*F. prausnitzii*) could restore the intestinal structure, which might be used as a potential therapeutic approach against inflammation as well as diabetes[94-96]. Furthermore, *F. prausnitzii* may serve as a diagnostic and therapeutic biomarker for the use of FMT[97]. The potential role of the gut microbiota has been hypothesized to modulate renal function in experimental DN murine models[98]. Through FMT, the role of the gut microbiota and its



**Figure 3** The gut microbiota could contribute to the favorable production of short-chain fatty acids, reactive oxygen species and D-amino acids against progression of diabetic nephropathy. Fecal microbiota transplantation consists of fecal microbiota infusion from a healthy donor to a recipient, which has been likely more successful than conventional therapy for diabetic nephropathy. Note that some critical events such as cytokine-induction have been omitted for clarity. SCFAs: Short-chain fatty acids; ROS: Reactive oxygen species; DN: Diabetic nephropathy; DM: Diabetes mellitus.

SCFA production have been verified in the treatment of DN. Therefore, administration of prebiotics and/or probiotics should individually be tailor-made to prevent and/or cure chronic diseases such as DN. For example, acetate produced by certain gut microbiota reprogramming has been shown to contribute to the tubulointerstitial injury of DN, suggesting that gut microbiota might be a new strategy for DN treatment[99]. Furthermore, FMT from healthy donors considerably attenuates glomerular injury with podocyte improvement in diabetic rats[100].

The above-mentioned topics are only just being explored in preclinical research, suggesting that further studies are required. Owing to a lack of treatments, DN has been a public health concern. Although it is untimely to draw definitive conclusions about the clinical usefulness of microbiota-based treatment strategies for DN, modulation of gut microbiota is an exciting frontier in kidney research. It is clear that intensive evaluation of preclinical studies is necessary to find further insights. In addition, long-term studies are also necessary to clarify the detailed effects of probiotic treatment in the management of DN. A healthy lifestyle with a balanced familiar diet is now one of the main recommendations.

## FOOTNOTES

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