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Gut Microbiota and Diabetic Kidney Diseases: Pathogenesis and Therapeutic Perspectives

Gut Microbiota and Diabetic Kidney Diseases

Jiaran Lin, Ziting Wang, Jiaojiao Sun, Yingying Yang, Xuexin Li, Xinru Wang, Yue Shi, Yuanyuan Zhu, Ruiting Wang, Mina Wang, Feiyu Xie, Peng Wei, Zehuan Liao

Abstract

Diabetic kidney disease (DKD) is one of the major chronic complications of diabetes mellitus (DM), as well as a main cause of end-stage renal disease. Over the last few years, substantial research studies have revealed a contributory role of gut microbiota in the process of diabetes mellitus and DKD. Metabolites of gut microbiota like lipopolysaccharide, short-chain fatty acids and trimethylamine N-oxide are key mediators of microbial–host crosstalk. However, the underline mechanisms of how gut microbiota influence the onset and progression of DKD are relatively unknown. Besides, strategies to remodel the composition of gut microbiota or to reduce the metabolites of microbiota have been found recently, representing a new potential remedial target for DKD. In this mini-review, we are addressing the possible contribution of the gut microbiota in pathogenesis of DKD and its role as a therapeutic target.

Key Words: Diabetes; Gut Microbiota; Insulin Resistance; Diabetic Kidney Disease; Pathogenesis; Therapeutic Targets

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Core Tip: This minireview consolidates the potential role of gut microbiota in the pathogenesis and as therapeutic targets of diabetic kidney disease. It is known that metabolites of gut microbiota such as trimethylamine N-oxide, short-chain fatty acids and lipopolysaccharides are important mediators of microbial-host crosstalk. However, the main mechanism of how the gut microbiota specifically affects the occurrence and progress of DKD has not yet been fully explored.

INTRODUCTION

DM continues to be one of the most challenging and economically costly diseases in the world, with its prevalence and incidence increasing[1]. About 20-40% of the affected population will develop into DKD[2], which is the primary contributor of end-stage renal disease (ESRD). The global incidence rate of diabetes in 2019 was expected to be 9.3% (463 million people) and may rise to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045[3-5]. The direct health expenses worldwide on diabetes in 2019 were predicted to be USD 760 billion and are projected to increase to 825 billion dollars by 2030 and 845 billion dollars by 2045[6]. The concern is that the prevalence of diabetes might continue to build up due to significantly expanded incidence of childhood obesity.

DKD can occur in type 1 diabetes, type 2 diabetes, and other secondary diabetes. The development of moderately increased albuminuria in patients with type 1 diabetes typically occurs 5 to 15 years after diabetes initiation and progresses through time[7, 8]. In a systematic review encompassing nine longitudinal studies of 7938 patients with type 1 diabetes and moderately increased albuminuria, the total incidence rate of moderately increased albuminuria was 28% over the mean 15-year duration of diabetes[9]. In comparison to patients with normoalbuminuria, the relative risk for all-cause mortality was 1.8 (95%CI 1.5-2.1), with a suggestion of a similar relative risk for cardiovascular mortality[9, 10]. Among nearly 5100 patients with type 2 diabetes included in the United Kingdom prospective diabetes study (UKPDS)[11], regarding the occurrence and progression of nephropathy, the results are reported as follows: ten years after the diagnosis of diabetes, the percentages of moderately elevated, severely elevated urine albumin, and plasma creatinine concentrations elevated to >175 μmol/L (2.0 mg/dL), or requiring kidney substitution treatment were 25%, 5%, and 0.8%, correspondingly.

The human gut nurtures more than 100 trillion microbial cells. The functional gut microbiota serves particular roles in many metabolic aspects of the host, including nutritional metabolism, alloangian and medicinal metabolism, maintaining the integrity of the intestinal mucosal barricade structure, immune regulation, as well as

resistance to pathogens [12]. Microbial cells are susceptibility factors for the development of nephropathy in individuals with the predisposition of nephropathy, such as patients with DM[13, 14]. The intestinal flora may influence the development and progression process of DKD by modifying the endocrine functions of the gut and the components of microbial metabolism products, and vice versa. Besides, hyperglycemia and progressive kidney disease determines alterations of the gut microbiota[15, 16].

In this article, we review the quantitative and qualitative changes in the gut microbiota of DKD patients that lead to this symbiotic disorder and how it contributes to the progression of DKD, and review well-targeted interferences that can reconstruct the symbiotic relationship.

DKD: PATHOGENESIS

DKD is a complicated and miscellaneous disease with numerous interrelated etiologic pathways. Patients with DKD have four main glomerular histopathological changes: mesangial expansion, glomerular basement membrane (GBM) thickening, podocyte effacement and glomerular sclerosis. It was believed that these histopathological changes were mainly due to the metabolic and hemodynamic disorders found in diabetes. Hemodynamic derangements are defined as the hyperfiltration which is due to vasoconstriction of efferent arteriolar following the activation of renin-angiotensin-aldosterone system (RAAS) under the stimulation of hyper glycemia. Nevertheless, in recent years it has become more and more apparent that despite the irrefutable central role of hyperglycemia in the development of DKD, it is not the only contributor to DKD. In general, the development of DKD involves several pathophysiological pathways including hemodynamic pathways, metabolic pathways, inflammatory pathways and autophagy pathways.

The changes in renal hemodynamic are partially regulated by vasoactive hormones, especially angiotensin II (Ang II) and endothelin (ET). In cultured rat mesangial cells, glucose increases Ang II production in a concentration-dependent

manner, which results in stimulation of transforming growth factor-β1 (TGF-β1) secretion, decreased matrix degradation, and increased matrix accumulation[17]. Temporary blocking the prediabetic rats' renin–angiotensin system for 7 weeks resulted in sustained reduction in collagen accumulation and gene expression of connective tissue growth factor (CTGF), which mediates downstream events of TGF-β and stimulates fibroblast proliferation and extracellular matrix (ECM) protein synthesis [18, 19]. In response to various factors, mesangial cells can release ET-1 and ET receptors, activation of which leads to a complex signaling cascade with resultant stimulation of mesangial cell hypertrophy, proliferation, contraction, and ECM accumulations[20].

The metabolic pathways including four different entities: the polyol pathway, hexosamine pathway, production of advanced glycation end products (AGEs), and activation of protein kinase C (PKC)[21]. Aldose reductase is the first enzyme in the polyol pathway. Studies have shown that the hemodynamic changes caused by early diabetes and the increase in vascular albumin infiltration and urinary albumin excretion are phenomena associated with aldose reductase[22]. The hexosamine pathway originates in the third phase of glycolysis, where fructose-6-phosphate is transformed into glucosamine-6-phosphate. Glucosamine-6-phosphate later is utilized as a substrate which augments the transcription of the inflammatory cytokines tumor necrosis factor-α (TNF-α) and TGF-β1[23], which we will discuss in the inflammatory pathways later. Tissue protein glycosylation is also one of the causes of diabetic nephropathy and other microvascular complications. In a long-term hyperglycemia state, part of the excess glucose will bind to free amino acids in the circulation or tissue proteins. The non-enzymatic reaction initially forms reversible early glycosylation products, and then forms irreversible AGEs. Long-term infusion of AGE-albumin to non-diabetic animals led to glomerular enlargement, GBM hyperplasia, mesangial ECM swelling, and albuminuria, which are all consistent with the glomerulopathy analogous to DKD[24]. Hyperglycemia-induced PKC activation in cultured mesangial cells or diabetic glomeruli is associated with a number of aberrations, namely, elevated arachidonic acid

secretion and prostaglandins synthesis, elevated expression of fibronectin, α1(IV) collagen and TGF-β1, and depressed Na+K+-ATPase action[25].

Various growth factors and cytokines may affect renal function directly or indirectly perform their actions by stimulating other factors. As mentioned before, in cultured mesangial cells, high glucose or Ang-stimulated production of matrix proteins is partially regulated by TGF-β. The mechanisms involve suppression of matrix metalloproteinase (MMP) synthesis, incentive of metalloproteinase inhibitor production and enhanced CTGF expression, etc [19, 26]. The expression of vascular endothelial growth factor (VEGF) is pronounced in quite few cells including glomerular visceral epithelial cells and tubular epithelial cells, where VEGF is able to induce a proliferative and an antiapoptotic response [27]. The direct evidence of VEGF is a mediator of DKD was collected from research, in which the weight of the kidney, the glomerular volume, the thickness of basement membrane (BMT) rose while urinary albumin excretion (UAE) descended in VEGF antibody-treated db/db mice.VEGF antibody administration tended to reduce expansion in total mesangial volume [28]. Each cytokine has several different effects. IL-1 takes a part in the progression of intra-glomerular hemodynamic aberrations associated with prostaglandin production by mesangial cells and can directly increase vascular endothelial cell permeability [29, 30]. The expression of renal IL-6 positively correlates with mesangial hyperplasia and tubular atrophy in various kidney disease models[31]. IL18 triggers the secretion of interferon gamma and results in producting additional inflammatory cytokines including IL1 and TNF, over-expression of adhesion molecules, as well as inducing endothelial cell apoptosis[32]. TNF is recognized to play a crucial part in the pathogenesis of DKD. TNF is not only cytotoxic to kidney cells, which can induce direct kidney damage, but also involved in processes such as the induction of apoptosis and necrotic cell death[33]. Studies have shown that TNF plays an important part in the progression of kidney hypertrophy and hypofunction, which are the 2 major changes in the preliminary stages of DKD, indicating that renal level of TNF may even have the potential to be used as a marker for early stage of DKD[34].

Autophagy (originating from the Greek word meaning " self-eating") is a basic cellular procedure sending intracellular components to lysosomes to be degraded in order to sustain homeostasis and cellular integrality[35]. Podocytes had a high basal level of autophagy. However, diabetic condition *in vivo* and high glucose conditions *in vitro* impaired autophagy, resulting in lysosome dysfunction and apoptosis, as well as autophagy defects leading to podocyte damage [36]. Because the dynamics of endoplasmic reticulum (ER) appeared to have a crucial function in modulating autophagic fluxes, ER cytoprotective capacity might fail under high glucose-induced unrelieved stress and cause autophagy disruption, speeding up the deterioration of DKD[37].

The components and activeness of the intestinal flora are symbiotic with the host since birth and are contingent on complex interactions which depends on the host genome, nutrition, and lifestyle. The gut microbiota plays an important role in maintaining the gut in normal individuals and human health as a whole, and its disfunction is tightly correlated with the occurrence of DM and the progression to DKD. MGWAS analysis showed that patients with T2DM are distinguished by moderate dysbiosis of the intestinal microflora, for example, by decreased abundance of some prevalent butyrate-producing bacteria, including Clostridium difficile SS3/4, Escherichia coli, Prevotella, Roscoidium intestinalis, and Roscoidium chrysogenum, as well as by an elevated number of diverse potential pathogens, including *Bacteroides caccae*, *Clostridium hathewayi*, *Clostridium ramosum*, *Clostridium symbiosum*, *Eggerthella lenta* and *Escherichia coli*, on top of which, there is an enrichment of the identified mucin-degrading species Akkermansia muciniphila and sulphate-reducing species *Desulfovibrio sp. 3_1_syn3* [38]. Several high quality data from the US Human Microbiome Project (HMP) [39], European Metagenomics of the Human Intestinal Tract (Meta HIT) [40] and several other researches have proven the favorable effects of the balanced intestinal flora on health all the way to the genetic layer, while Tao et al. Scientists revealed that the abundance of the intestinal microflora and the degree of diversity of bacterial groups were significantly different in DM with respect to healthy

controls, and DKD with respect to DM. Interestingly, the variables of g_Prevotella_9 (AUC=0.9) allowed precise identification of DM from age- and sex-matched healthy controls, and the variables of g_Escherichia-Shigella and g_Prevotella_9 (AUC=0.86) allowed precise identification of DKD from age- and sex-matched DM patients [41].

The gut microbiota participates in the regulation of various host metabolic pathways. Disorders of the gut environment and associated variations in the makeup of the gut microflora as well as the metabolites produced by which, represent a condition referred to as "intestinal dysbiosis" [42, 43], leading to disorders of interactive host-microbiota metabolism, signal transduction, and immune-inflammatory axes and influence the gut, liver, kidney, muscle, and brain through physiological connection, thus may trigger a systemic inflammatory response. Under normal circumstances, the gut barricade precludes the transfer of substances and microorganisms from the intracavity to the bloodstream; the gut barricade is composed of distinct constructions/systems: tight junctions, intestinal epithelial cell membranes, mucus secretion, and immune defensive mechanisms of the gut lining [42, 44]. However, intestinal dysbiosis may result in a "leaky gut syndrome", with increased permeability that enables the the leakage of pro-inflammatory bacterial products for instance lipopolysaccharide (LPS),contributing to insulin resistance [45] as well as expediting the development of renal disorders in people with diabetes [14]. Microbial metabolites are essential intermediaries of microbial host crosstalk, engaging in the regulation of host metabolism and gut integrity.

Endotoxin, a phospholipid, is the hydrophobic anchor of LPS which comprises the external layer of the majority of Gram-negative bacteria. Salguero et al. revealed a significant relevance between the dysbiosis of Gram-negative bacteria which includes increasing relative abundance of *Proteobacteria*, *Verrucomicrobia* and *Fusobacteria*, raised LPS concentrations, and accumulated state of inflammation biomarkers consisting of CRP, TNFα and IL-6 in DKD patients in contrast to the controls [46]. Also, as a result of the leaky gut syndrome, LPS translocation which leads to a high circulating levels of LPS, a condition known as "endotoxemia", stimulates immune system cells, especially

macrophages and endothelial cells. In macrophages, LPS activates IL-1R-associated kinase (IRAK) through TLR4-mediated signaling by MyD88 and MD2, with ensuing induction of TNF receptor-associated factor 6 (TRAF6) binding with IRAK and other proteins forming a large complex, catalyzing the synthesis of a Lys 63-linked polyubiquitin chain of TRAF6 and finally resulting in the activated transcription factor NF-κB and discharged pro-inflammatory cytokines [47], which is known to be important in the pathogenesis of DKD [48].

Hallmark features of gut dysbiosis is a decrease in the levels of short chain fatty acids (SCFA) - producing saccharolytic microbes. SCFAs are the end products of fermentation of dietary polysaccharides by intestinal microbiota, including acetate, propionate, butyrate, pentanoic acid and isobutyric acid[49]. The functions of SCFAs are generally concerned with the activation of transmembrane G protein-coupled receptors (GPR) and the repression of histone acetylation (HDAC) [50]. increase glucagon-like peptide-1 (GLP-1) and GLP-2 production through GPR stimulation, along with elevated insulin expression and ensuing augmented insulin sensitivity and proliferation of pancreatic s-cells. Intriguingly, glucose homeostasis and feelings of satiety are both regulated by gut microbiota components like *Bifidobacterium* and *Lactobacillus* that enhances GLP-1 secretion [51]. Besides, SCFAs can inhibit oxidative stress and inflammation of glomerular mesangial cells (GMCs) induced by high glucose and LPS [52], as well as improve intestinal barrier function [53]. Sodium butyrate treatment markedly reduced the level of glucose, creatinine, urea in plasma, attenuated histological changes, involving fibrosis and collagen deposition, and curbed the activity of HDACs, eNOS, iNOS,fibronectin, TGF-β1, NF-κB, apoptosis, and DNA damage in diabetic kidneys [54]. However, not all the remedies of SCFAs showed favorable effects. Lu et al. discovered aberrant intestinal flora, elevated plasma acetate levels, raised proteinuria, thickened GBM, and loss of renal podocyte foot process in DM rats compared to control rats[55]. In addition, the amount of angiotensin II, angiotensin-converting enzyme, and angiotensin II type1 receptor boosted in DM rats' kidneys, suggesting that redundant acetic acid produced from gut flora disorders may cause

kidney damage by activating RAAS in the kidney.It is hypothesized that these differences of SCFAs studies may result from disparate animal models in disparate diseases but also from the group, concentration, and timing of application of SCFAs.

Imbalance of the gut microbiota is also a potential source of uremic toxins. Urea is derived in the liver from the urea cycle and its origin is dietary/endogenous amino acids and their decomposition in the peripheral tissues. The intestinal microbiota uses urease to convert urea into ammonia (NH3) and carbon dioxide. A portion of the ammonia goes through the urea cycle in liver and is transformed back into urea, whereas the rest of the ammonia is transformed into ammonium hydroxide (NH4OH) and then excreted from the body with feces [13]. Changes in lifestyle, diet as well as reduced fiber consumption can cause imbalance in the intestinal flora and production of an overload of the uremic toxins (e.g., indoxyl sulfate (IS), phenyl sulfate (PS), p-cresyl sulfate (PCS), and trimethylamine-N-oxide (TMAO)). Normally, The amount of IS receptors (aryl hydrocarbon receptors (AhRs)) may modulate podocyte functionality. Nevertheless, under conditions of imbalanced intestinal flora, AhRs are prolonged activated by broad exposure to IS, which results in progressive damage of podocytes and glomeruli including altered cell morphology, elevated levels of expression of pro-inflammatory cytokines and chemokines, declined podocyte differentiation, and reduced expression of cytoskeletal proteins [56]. Also, AhR was demonstrated interacting with various signaling molecules such as NF-κB, which is responsible for the upregulation of proinflammatory proteins in uremic conditions [57]. Kikuchi et al. found that the amount of PS (a intestinal microflora-derived metabolite) increased with advancing diabetes in rats in which the human uremic toxin transporter SLCO4C1 was over-expressed in the kidney, whereas it declined in rats that showed limited proteinuria. In pilot models of DM, the giving of PS triggers albuminuria and podocyte injury. In a cohort of DM patients, PS levels were closely related to the baseline and forecasted advancement of albuminuria in patients with microalbuminuria over 2 years [58]. Figure 1 illustrates the pathogenic associations between gut dysbiotic microbiota and development of diabetic kidney diseases from the gut-kidney axis.

THERAPEUTICS AGAINST GUT MICROBIOTA IN DKD

Exercise is considered to be an important potential factor in modification of gut microbiota, which could conduct both beneficial and harmful effects under some specific circumstances. Moderate level of exercise may be able to keep balance of gut microbiota and reduce harmful bacterium in the digestive tract to some extent [59]. However, Filipe M etc. found excessively intensive exercise may lead to increased permeability in digestive tract [60].

Obviously, the host genome is the main risk determinant for a number of different diseases. Nonetheless, not alike the host genome, the genome of microorganisms in the host can be changed. Through the administration of prebiotics (dietary foods that boost the growth or performance of particular microorganisms), probiotics (live bacteria), synbiotics (mixtures of probiotics and prebiotics), as well as antibiotics, people are able to alter the composition of the intestinal microbiota themselves and thereby modify the resultant metabolites.

Animal studies found that high-fat-fed diabetic mice treated with prebiotics (fructo-oligosaccharides, FOS) not only had a higher level of intestinal *Bifidobacterial* and colonic GLP-1 precursor, reduced endotoxaemia, but also obtained improvement on their glucose tolerance and insulin resistance [61]. This dietary shift method also worked in germ-free mice colonized with a synthetic community where at day 35 (7 days following the change to the FOS diet), there was a distinct decline in *Bacteroides caccae* enrichment and a concurrent increment in *B. caccae* enrichment. Of importance, during the same period, there was a significant reduction in the level of IS in the host, and this decrease remained unchanged after 1 week, suggesting a steady drop in the production of uremic toxins [62]. Li et al. reported that feeding diabetic rats with a high-fiber diet, and feeding diabetic control rats with a normal diet or a zero-fiber diet, the former was less likely to fall into the DKD phase featured with albuminuria, glomerular hypertrophy, podocyte injury, and interstitial fibrosis. Fiber can profitably reshape intestinal microbial ecosystem and improve microecology dysbiosis. For example, fiber

allowed growth in density of fecal and systemic SCFA through stimulating the colonization of SCFA-producing bacteria such as the genera *Prevotella* and *Bifidobacterium*. Besides, fiber may intervene the progression of DKD by diminishing the expression of genes which are responsible for the generation of inflammatory cytokines, chemokines, and fibrosis-promoting proteins. SCFAs were nephroprotective in diabetic mice, providing that GPR43 or GPR109A is present. In vitro cellular experiments revealed that SCFAs could regulate hyperglycemia-induced inflammation in renal tubular cells and podocytes[63].

Bohlouli et al. analyzed data from 340 DKD patients by systematically reviewing and quantitiatively synthesizing 7 RCTs. They found that probiotics consumption beneficially impact the inflammation and oxidative stress biomarkers by significantly reducing high-sensitivity C-reactive protein(hs-CRP) and malondialdehyde (MDA) plus increasing glutathione (GSH) and total antioxidant capacity (TAC) in subjects. Yet probiotics had no remarkable effect on concentrations of nitric oxide (NO). Subgroup analysis indicated that when the probiotic dosage was greater 5 billion CFU per day, the total impact of probiotics on serum TAC concentrations was more prominent[64]. Vlachou et al. concluded that most studies showed the beneficial effects of supplementary probiotics in decreasing inflammation, oxidative stress and improving biomarkers of the kidney functions in DKD patients, and the majority of microbes applied in the researches were in the genera of *Lactobacillus* and *Bifidobacterium*. Doses varied from 2×10^7 to 6×10^{10} CFU/ g. The format of the probiotics differed among projects (capsules, pouches, soy milk, yogurt and honey) [65]. Probiotics use may also help to reinforce the barrier function, through prevention of dysbiosis and the regulation of cytoskeletal and tight junctional protein phosphorylation. Guo et al. illustrated that *Bifidobacterium infantis* and *Lactobacillus acidophilus* was able to safeguard the gut barrier from irritation by IL-1β and thereby preserving the intestinal permeability to an extent. The mechanism may be that the level of occluding and claudin-1 was normalized and that the IL-1β-induced NF-κB activation was inhibited in Caco-2 cells[66]. Resta-Lenert et al. remarked that when the epithelial cell lines were

under the exposure of enteroinvasive *Escherichia coli* (EIEC), the application of *S. thermophilus* and *L acidophilus* could sustain and sometimes even strengthen the structures of cytoskeleton and tight junction proteins[67].

There are relatively few studies on synbiotics in DKD. In a randomized, double-blind and placebo-controlled trial encompassing 81 DM patients, the consumption of synbiotic bread containing *Lactobacillus sporogenes* and inulin caused a marked increment in levels of NO in the blood plasma and a remarkable drop in MDA concentrations compared to the probiotic and control breads. But there was no significant influence of probiotic bread intake on levels of TAC, GSH, catalase in plasma, liver enzymes, calcium, iron, magnesium in serum and blood pressure in contrast to probiotic and control breads [68]. There is another study where patients with ESRD who are undergoing haemodialysis (HD) received synbiotic (*Lactobacillus casei* strain Shirota and *Bifidobacterium breve* strain Yakult as probiotics and galacto-oligosaccharides as prebiotics) for 2 weeks. The results of the study demonstrated p-cresol is a constipation-related uraemic toxin, and the three subjects with the highest serum p-cresol level were diabetic HD patients. The synbiotic regimen regularized defecation habits and reduced serum level of p-cresol in HD patients [69].

Hu et al. found out that depletion of gut microbiota treated by antibiotics significantly alleviated tubulointerstitial injury, reduced IL-6 concentrations in the blood, as well as efficiently relieved glycemia in DM rats. Meanwhile, it rescued the increased urine albumin creatinine ratio and N-acetyl-β-D-glucosidase (NAG) creatinine ratio. Intriguingly, in DM rats treated with antibiotics, the levels of acetate in the serum also declined significantly and were positively correlated with kidney cholesterol concentrations [70]. Similar results were found in diabetic rats by using broad-spectrum antibiotics, where not only the majority of the intestinal microbiota was thoroughly killed, but also the concentrations of acetate in plasma were reduced, intrarenal RAAS activation was effectively suppressed, and renal injury was mitigated[55]. Antibiotic therapy is unable to eliminate every microorganism that exists in the intestine of mice, however, it is possible to maintain the microbiome in quite low

levels, which is why antibiotic therapy is commonly applied to acquire pseudo-germ-free mice in gut microbiota studies even if the requirement of germ-free mouse maintenance is rigid and difficult to fulfil in most laboratories. Nevertheless, a large amount of antibiotics may damage the kidneys of mice. Moreover, the use of antibiotics alone is not the best solution, because of the possible consequences of microbiome abatement, for example, antibiotic-related pathogen aggression [71]. The sensible application of antibiotics to achieve or enforce selection of strains colonized with specific metabolic traits is likely to present a plan that can achieve shrinkage of toxin production and preservation of many of the microbiota's health benefits.

A more sustained and potent treatments to reconstruct a robust microbiome structure and functionality might include contiguous fecal microbiota transplantation (FMT) originating in healthy donors. Bara et al. found that FMT from healthy mice improved PCS accumulation, glucose tolerance and albuminuria [72]. Reconstructing a "healthy microbiota" in patients shows great promise for rebuilding gut, immune and metabolic homeostasis and it has been tested to be secure and well-tolerated in previous clinical trials [73, 74].

CONCLUSION AND PERSPECTIVES

Gut microbiota serves as a central part as the regulator in metabolic and inflammatory homeostasis, functioning as a link between the host and environmental influences. Constituent of the intestinal microbiota in DKD patients varies from that of the healthy population. Both animal and human studies have confirmed the correlation of gut dysregulation with DKD and associated metabolic disorders. Several studies have shown budding therapeutics against gut microbiota on glucose tolerance, insulin resistance, gut barrier integrity, endotoxaemia, uremic toxin, SCFA, TAC and so forth, which may breed new methods for the prevention and treatment of DKD and relevant metabolic diseases. Howbeit, which gut microbiota constituents are the causes of renal injury and aberrant glucose metabolism, and which are conservational factors against kidney damage and metabolic disorders, are still being scrutinized, so the systematic

application is not currently recommended for DKD treatment and related metabolic derangement. The dose, time length of treatment, and prolonged outcomes of the utilization of various colonies still call for further investigation; extra searches are demanded before gut microbiota therapies can be judiciously assigned for the treatment or prevention of DKD. Diet modification, lifestyle modification, and control of environmental factors are still pivotal strategies to prevent DKD progression. Our understanding of this gut-kidney crosstalk remains rudimentary, even though there is rapidly accumulating information. Additional work is needed to describe the patho-physiological elements of this interrelationship and to invent new treatments strategies to counteract a detrimental loop of DKD-gut dysbiosis which drives renal disorders to ESRD.

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