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Review

Review

Enterorenal crosstalks in diabetic nephropathy and novel therapeutics targeting the gut microbiota

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Abstract

The role of gut-kidney crosstalk in the progression of diabetic nephropathy (DN) is receiving increasing concern. On one hand, the decline in renal function increases circulating uremic toxins and affects the composition and function of gut microbiota. On the other hand, intestinal dysbiosis destroys the epithelial barrier, leading to increased exposure to endotoxins, thereby exacerbating kidney damage by inducing systemic inflammation. Dietary inventions, such as higher fiber intake, prebiotics, probiotics, postbiotics, fecal microbial transplantation (FMT), and engineering bacteria and phages, are potential microbiota-based therapies for DN. Furthermore, novel diabetic agents, such as glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium-dependent glucose transporter-2 (SGLT-2) inhibitors, may affect the progression of DN partly through gut microbiota. In the current review, we mainly summarize the evidence concerning the gut-kidney axis in the advancement of DN and discuss therapies targeting the gut microbiota, expecting to provide new insight into the clinical treatment of DN.

Key words diabetic nephropathy, gut microbiota, microbiota-derived metabolites, GLP-1 receptor agonist, DPP-4 inhibitor, SGLT-2 inhibitor

Introduction

The human gastrointestinal tract hosts a mass of microbiota, which encodes a genome 150-fold larger than human genes and is considered the "second" human genome. These microbiomes influence the physiological metabolism of the human body through interaction with the environment and the human genome and actively perform structural and histological functions [1]. The main functions of metabolism, immunity, and endocrine in the host are related to gut microbiota [2]. Under normal conditions, the gut microbiota is relatively stable, maintaining symbiotic and antagonistic relationships in the intestinal tract. When the composition of gut microbiota changes, in the case of changes in nutritional status, morbid state, and other factors, the balance of the microbiota breaks, namely, dysbiosis of the bacterial community [3,4]. Dysbiosis of the gut microbiota can affect insulin resistance (IR), bile acid (BA) metabolism, inflammatory response and intestinal permeability, which is closely related to the occurrence and development of diabetes [5,6]. Impaired intestinal permeability is one of the causes of systemic inflammation. This chronic low-grade inflammatory state is considered a hallmark of diabetes and its complications, such as diabetic nephropathy (DN) [7]. Therefore, maintaining the diversity and balance of the intestinal microbiota is critical in regulating the health maintenance and homeostasis of the host.

DN is a kind of chronic kidney disease (CKD) and a common complication of diabetes mellitus (DM), which is the leading cause of end-stage renal disease (ESRD) in most countries and regions [8]. Notably, both type 1 diabetes (T1D) and type 2 diabetes (T2D) develop DN to some extent, with T1D appearing with a greater possibility [9]. The symptoms of DN are characterized by increased excretory proteinuria, progressively decreased glomerular filtration rate (GFR), ongoing intrinsic tubular injury, or endothelial/microvascular injury [10]. In addition, maladaptive repair and unopposed inflammation may also occur with the progression of DN [10]. Furthermore, urinary tract infections (UTIs) are common in diabetic patients and may aggravate the damage to renal function, suggesting their possible involvement in the pathogenesis of DN [11]. However, the mechanism of DN has not been fully elucidated. A series of recent reports indicate that the endothelial-

to-mesenchymal transition (EndMT) of glomerular endothelial cells plays a crucial role in DN, of which the role of lysine methyltransferase 5A (KMT5A) appears to be even more critical, as KMT5A is involved in the progression of DN by affecting inflammation, glycolytic processes, and endothelial injury [12–14]. Apart from the above and currently known molecular signaling, microbiota-derived metabolites such as short-chain fatty acids (SCFAs), secondary bile acids (BAs), and uremic toxins may also be involved [15–17].

Therefore, to clarify the pathogenesis of DN, we will first summarize the gut-kidney axis theory, including the changes in the renal barrier and intestinal permeability and the composition of gut microbiota in the progression of DN. Then, the effects of microbiota-derived metabolites, such as SCFAs, secondary BAs and uremic toxins, on the advancement of DN will be discussed. Finally, the impacts and possibilities of currently available novel diabetic drugs on DN targeting the microbiota will be reviewed.

The Gut-kidney Axis in DN

A growing body of evidence has indicated that the bidirectional crosstalk between the host and microbiota is pathophysiologically relevant in patients with CKD, the so-called gut-kidney axis [18] (Figure 1). Changes in gut microbiota in DN are usually manifested by an increase in the proportion of multiple pathogenic bacteria and a decrease in probiotics [19–22]. The gut-kidney axis theory illustrates that changes in the gastrointestinal tract or the kidney can affect the other side through the intestinal mucosa, microbiota, immune inflammation, and other aspects, resulting in adverse consequences [23]. These may be attributed to the severe impairment of renal function in the later stage, and the release of many nitrogen-containing products through the intestinal tract may cause the immense proliferation of intestinal pathogens which utilize these wastes, thereby aggravating the disorder of gut microbiota [24,25] (Figure 1). Meanwhile, the dysbiosis of microbiota and the impaired gut barrier function may also induce systemic inflammation through the endotoxins and metabolites of the microbiota, resulting in the deterioration of renal function (Figure 1).

Specifically, the kidney cannot entirely excrete numerous metabolic wastes in circulation, and as a result, they will accumulate. These wastes enter the intestinal lumen through the bowel wall, resulting in the imbalance of the intestinal microbiome and probiotic reduction. Consequently, the increase in toxic metabolites produced by intestinal microbes, such as indoxyl sulfate, p-cresol sulfate, and phenylacetylglutamine, accelerates the deterioration of renal function [26]. According to the experimental results of Vaziri *et al.* [24], patients with ESKD showed both a contraction of the bacterial family containing butyrate-producing enzymes and an expansion of the bacterial family producing indoles and p-cresyl. Just as uremia affects the composition and metabolism of gut microbes, critical uremic toxins are also derived from microbial metabolism [23]. Taken together, renal function damage is associated with microbiota disorders, and alterations in the gut microbiota, in

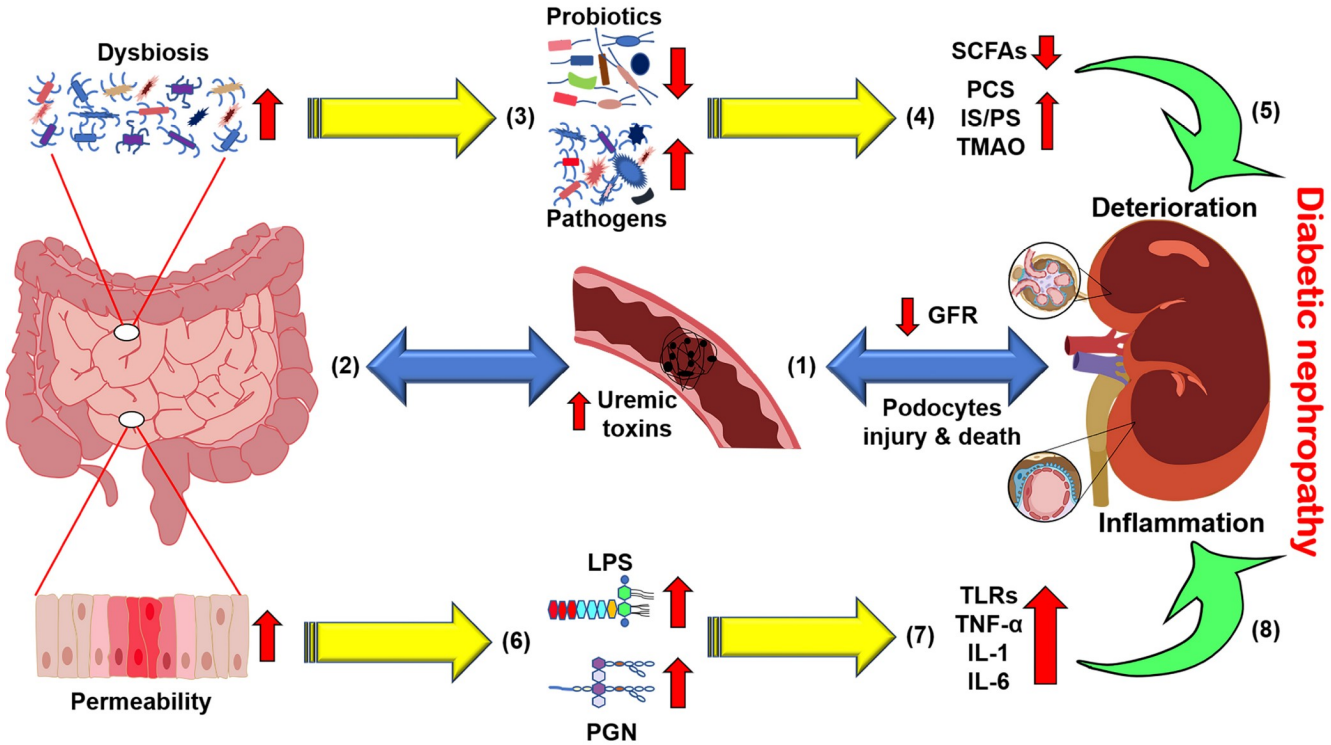

Figure 1. The gut-kidney axis in diabetic nephropathy (DN) With the manifestation of renal dysfunction, (1) glomerular filtration rate (GFR) decreases with podocyte damage and death, and (2) uremic toxins accumulate in the circulation and destroy the homeostasis of the intestinal microbiota, namely, dysbiosis. Subsequently, (3) pathogens utilizing nitrogenous waste are increased at the expense of fewer probiotics. (4) Short-chain fatty acid (SCFA) production decreases, while the levels of typical uremic toxins, such as p-cresyl sulfate (PCS), indolyl sulfate (IS), phenyl sulfate (PS) and trimethylamine N-oxide (TMAO), are increased, and (5) ultimately deteriorates DN. In addition, (6) changes in the intestinal microenvironment result in increased intestinal permeability, leading to the leakage of bacterial components such as lipopolysaccharides. (7) These endotoxins bind to signaling molecules such as toll-like receptors (TLRs) to recruit inflammatory cytokines and (8) cause chronic systemic inflammation in the kidney.

turn, continue to aggravate renal impairment (Figure 1).

Impairment of the renal barrier in DN

Podocytes are glomerular visceral epithelial cells that form the glomerular filtration barrier together with endothelial cells and the glomerular basement membrane (GBM) [27]. Podocytes are terminally differentiated cells with poor proliferative capacity and are highly vulnerable to injury. Excessive expression of Toll-like receptors (TLRs), such as TLR2/4, in DN patients could also cause podocyte injury and mesangial dilation, leading to kidney injury [15] (Figure 2). Once podocytes are damaged, they fall off from the basement membrane and are excreted with urine, which could damage the filtration barrier and produce albuminuria; meanwhile, damaged podocytes fail to compensate for the basement membrane, leading to glomerulosclerosis, a hallmark of DN [28].

In particular, the NLRP3 inflammasome complex actuates the production of active proinflammatory cytokines, while the expression of NLRP3 inflammasome-activating markers in the kidney is associated with the severity of albuminuria in patients with renal dysfunction [29]. More importantly, the administration of NLRP3 inhibitor MCC950 could normalize the urinary albumin-to-creatinine ratio (UACR) and ameliorate podocyte injury and renal fibrosis in *db*/*db* mice [30], suggesting the potential of NLRP3-targeted therapy in the treatment of DN (Figure 2). Furthermore, NLRP3 is an intracellular sensor that initiates inflammatory responses by detecting a broad range of microbial motifs, such as bacterial translocation in both the urethra and intestines [31]. Bacteriuria or abnormal urinary tract microecology caused by decreased GFR in DN may trigger an NLRP3-mediated inflammatory cascade that exacerbates the disease, including proteinuria, podocyte injury, and renal fibrosis.

UTI is a common complication in diabetic patients, and DN patients are more prone to UTI due to impaired renal function. More recently, there has been increasing concern about discovering and

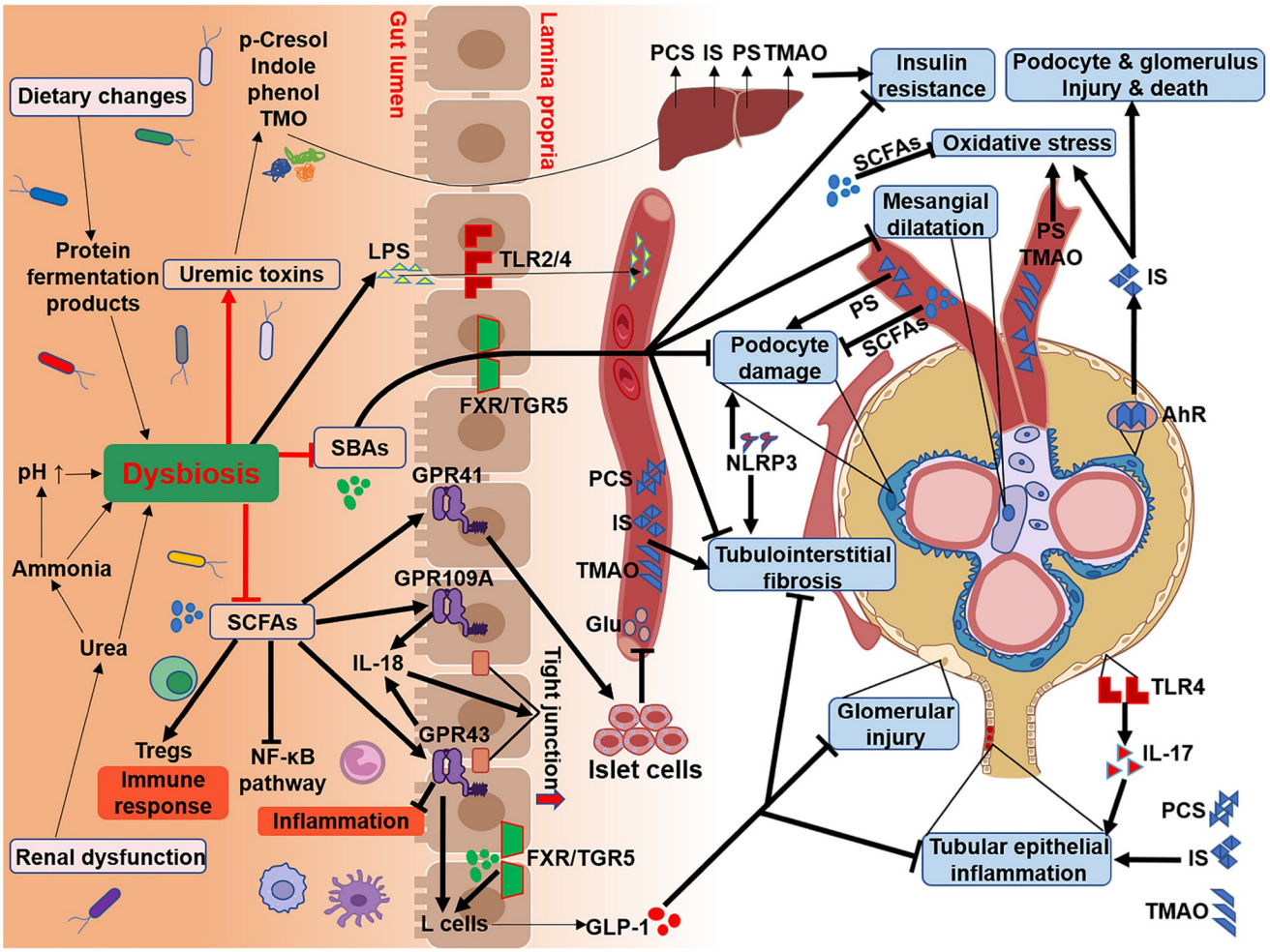

Figure 2. Gut microbiota-derived metabolites in the progression of DN Dysbiosis caused by renal dysfunction and dietary changes results in metabolic disorders. The immunomodulatory and anti-inflammatory effects of SCFAs, through regulatory T-cell cell (Treg) involvement and inhibition of the nuclear factor-κB (NF-κB) pathway, are suppressed due to the reduction in SCFA-producing bacteria. The weakening of renal protection by SCFAs through G-protein-coupled receptors (GPRs), such as preventing tubulointerstitial fibrosis, glomerular damage, and tubule epithelial cell inflammation, undoubtedly promotes the progression of DN. Secondary bile acids (BAs), by binding to its receptor FXR/TGR5, can improve DN by reducing podocyte damage and mesangial expansion, which are also restrained by the disturbance of the intestinal microbiota. The precursors of uremic toxins produced by colonic fermentation are transported to the liver to synthesize circulating uremic toxins, including PCS, IS, PS and TMAO, which steadily deteriorate DN through direct toxic activity and oxidative stress or damage to podocytes and glomeruli by binding to receptor AHRs.

measuring the relevance of the urinary microbiome to human health [32,33]. The urinary microbiome is significantly changed in DN patients with UTIs, while there is little direct evidence showing that the abnormal urinary microbiome influences the progression of DN. However, some indirect links are being explored. For example, the most common pathogens of UTIs, uropathogenic *E. coli* (UPEC), and other symbiotic bacteria that colonize the urinary tract, such as *Lactobacillus*, *Streptococcus*, and *Bifidobacteria*, metabolize the extracellular glycosaminoglycan (GAG) layer of the uroepithelium of the host, acting as a natural barrier [34]. As a result, urinary tract waste and microorganisms leak into the circulation, leading to the occurrence and deterioration of DN. Even though the mechanisms remain to be clarified, such as the cause-and-effect relationship between the glomerular filtration barrier and UTIs and the interaction of bacteria with GBM, maintaining the integrity of the renal barrier and stable urine microbiota may be a breakthrough for the prospective treatment of DN.

Intestinal permeability changes in DN

The intestinal tract is a significant barrier separating the microorganisms in the intestinal lumen from the internal environment (Figure 2). Numerous microbial systems interact with the internal environment through the intestinal wall so that they are isolated by the intestinal tract and confined to the lumen [35]. Alterations in the composition and function of the gut microbiota in DN patients lead to damage to the intestinal epithelial barrier and increased intestinal permeability [36]. Specifically, due to the decrease in renal filtration in DN patients, the reabsorption of ammonia increases from the hydrolysis of large amounts of urea, followed by the resynthesis of urea in the liver, which causes a marked decrease in transepithelial electrical resistance (TER) and loss of key tight junction proteins, such as claudin-1, occludin, and zonula occludens-1 (ZO-1) [37]. Ammonia can also be converted into ammonium hydroxide, thereby causing an increase in intestinal pH, aggravating the intestinal mucosal injury, and leading to epithelial barrier structure and function disorders [38] (Figure 2). Furthermore, the breakdown of intestinal epithelial tight junctions causes the entry of microbial components into the underlying tissue compartment, triggering a local inflammatory process that in turn leads to the persistence of intestinal barrier damage [39]. Cresol, indolinyl molecules and other toxins are then transferred to the blood, which induces systemic inflammation, further contributing to the pathogenesis of DN [40] (Figure 2).

Increased intestinal permeability could lead to sustained infiltration of lipopolysaccharide (LPS) into the portal vein, resulting in metabolic endotoxemia and increased levels of inflammatory cytokines that accelerate the progression of DN [41]. LPS is the surface antigen of gram-negative bacteria, which mediates host inflammation via TLR2- and TLR4-related pathways [42] (Figure 2). Studies have revealed that TLR2 and TLR4 are involved in the continuous inflammatory response process of DN by inducing the release of proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and IL-6, and the activation of the nuclear factor-κB (NF-κB)-mediated inflammatory cascade reaction [43] (Figure 2). Upregulation of TLR4 expression in glomeruli of the early stage of DN could lead to elevated levels of IL-17 and urinary albumin, thereby exacerbating chronic inflammation of DN[44], which might be a good predictor of renal function decline in DN (Figure 2).

Intestinal dysbiosis in DN

As mentioned above, patients with DN are associated with microbiota dysbiosis (Table 1). The decrese in the relative abundance of probiotics such as *Bifidobacterium*, *Lactobacillus* and *Prevotella* and the increase in the number of pathogenic bacteria such as *Coprobacillus* and *Desulfovibrio* confirm the imbalance of gut microbiota in rodent models with DN [15,19,45] (Table 1). Li *et al.* [21] found that *Allobaculum* and *Anaerosporobacter* aggravate renal function deterioration in DN, while *Blautia* may play a protective role in mice. Similar changes were found in mice with acute kidney injury (AKI) [46,47]. In addition, changes in microbiota that are related to uremic toxins could also be detected in patients with renal disease, represented by the anaerobic gram-positive families *Christensenellaceae*, *Lachnospiraceae* and *Ruminococcaceae* [48]. Butyrate-producing bacteria, *Roseburia* and *Faecalibacterium*, are negatively associated with renal function in patients [49–51] (Table 1). A recent study showed that DN patients had reduced intestinal microbiome richness compared to healthy subjects; specifically, *Coriobacteriaceae* was enriched in DN subjects, while *Prevotellaceae* was the most abundant bacteria in healthy individuals [20]. The researchers also found that the level of *Prevotella_9* could be an accurate predictor of diabetic individuals by analyzing the microbiological differences among the diabetic patients, DN patients, and healthy controls [20]. Compared to diabetic patients without renal complications, DN patients could be accurately distinguished by *Escherichia-Shigella* and *Prevotella_9* variables, with the former notably increased and the latter significantly decreased [20]. Other studies have reported that *Enterobacteriaceae* are more abundant in the DN patients than in healthy individuals [24,50] (Table 1). In addition, the increased relative abundance of *Enterobacteriaceae* might also be associated with the inflammatory response, as they express effective immune stimulants, such as LPS and peptidoglycans (PGNs) [52,53] (Figure 2).

On the other hand, the murine model of DN showed a declining *Firmicutes*/*Bacteroides* (F/B) ratio [21], and the level of *Firmicutes* was negatively correlated with the degree of kidney damage in DN, which seemed to conflict with the current view that increased F/B ratios indicated poorer health conditions [54]. The F/B ratio in healthy mammals is relatively stable, and an increase or a decrease in the F/B ratio may represent a disease state. However, whether it is a disease state can no longer be judged based simply on the ratio of F/B, and more data are needed to clarify the precise role of F/B. Although animal models cannot adequately represent disease progression in humans, these findings provide substantial evidence for the indispensable role of gut microbiota in DN.

Gut Microbiota-derived Metabolites in the Progression of DN

SCFAs

SCFAs stimulate the proliferation of epithelial cells and play an essential role in preventing and treating metabolic disorders, of which acetate, propionate and butyrate are the most abundant [55,56] (Figure 2). The major butyrate-producing bacteria in the gut belong to the phylum Firmicutes, particularly *Faecalibacterium prausnitzii* and *Roseburia spp.*, as well as *Clostridium leptum* [49–51]. In addition to butyrate, the production of other SCFAs is mediated by strains involved in carbohydrate fermentation processes, such as *Bifidobacterium* [57].

It has been reported that acetate and butyrate partially ameliorate

Table 1. Changes of gut microbiota composition in renal diseases

Subject	Changes in gut microbiota			Functional effects and/or relevance	Reference
	Phylum level	Family level	Genus/species level		
Mice with diabetic nephropathy	*Actinobacteria*↑	Unknown	*Prevotella*↓, *Bifidobacterium*↓, *Rikenella*↓, *Ruminococcus*↓, *Bacteroides acidifaciens*↓	Related to SCFAs production	15
Rats with diabetic nephropathy	*Actinobacteria*↑, *Firmicutes*↓, *Proteobacteria*↓	*S24-7*↓	*Turicibacter*↑, *Coprobacillus*↑, *Prevotella*↓, *Clostridium*↓, *Ruminococcus*↓, *Oscillospira*↓	Associated with the progression of diabetic nephropathy	19
14 T2DM patients with diabetic nephropathy	Unknown	*Coriobacteriaceae*↑, *Prevotellaceae*↓	*Escherichia-Shigella*↑, *Prevotella_9*↓	Contributed to the physiopathological diagnosis of DN from DM	20
Mice with diabetic nephropathy	*Firmicutes*↓	Unknown	*Anaerosporobacter*↑, *Allobaculum*↑, *Blautia*↓	Gut flora may contribute to the heterogeneity of the induced response	21
Rats with diabetic nephropathy	Unknown	*Coriobacteriaceae*↑, *Erysipelotrichaceae*↑	*Adlercreutzia*↑	Related to proteinuria in diabetic nephropathy	22
Rats with diabetic nephropathy	Unknown	*Peptostreptococcaceae*↑, *Rikenellaceae*↓, *Ruminococacceae*↓	*Turicibacter*↑, *Desulfovibrio*↑, *SMB53*↑, *Clostridium*↓, *Lactobacillus*↓	Related to the metabolic disorder of diabetic nephropathy	45
24 patients with ESRD and uremic animals	*Actinobacteria*↑, *Firmicutes*↑, *Proteobacteria*↑	*Brachybacterium*↑, *Enterobacteriaceae*↑, *Thiothrix*↑, *Halomonadaceae*↑, *Nesterenkonia*↑ *Lactobacillaceae*↓, *Prevotellaceae*↓	Unknown	Changes in the biochemical environment caused by uremia and its therapeutic intervention	24
Mice with bilateral I/R injury	Unknown	*Enterobacteriaceae*↑, *Ruminococacceae*↓	*Lactobacilli*↓	The hallmarks of I/R induced dysbiosis, associated with SCFAs reduction and intestinal inflammation	46
Mice with unilateral I/R injury	Unknown	Unknown	*Clostridium*↑, *Ruminococcin*↑, *Bifidobacterium*↓, *TM7*↓	Related to D-Serine/L-Serine level and tubular damage/ tubular cell proliferation	47
855 individuals with early renal function decline	Unknown	*Christensenellaceae*↑, *Ruminococcaceae*↑, *Lachnospiraceae*↑	Unknown	Related to circulating metabolites derived from bacterial protein fermentation and eGFR	48
65 patients with CKD	Unknown	Unknown	*Roseburia spp.*↓, *Faecalibacterium prausnitzii*↓	Butyrate-producing bacteria are negatively associated with renal function	49
892 adults with kidney disease/52 patients with ESRD	*Proteobacteria*↑, *Verrucomicrobia*↑, *Actinobacteria*↓	*Enterobacteriaceae*↑, *Streptococcaceae*↑, *Prevotellaceae*↓	*Streptococcus*↑, *Prevotella*↓, *Prevotella 9*↓, *Roseburia*↓, *Faecalibacterium*↓, *Clostridium*↓, *Coprococcus*↓	Uremic toxin generation in adults with kidney disease at the expense of producing less butyrate	50, 51

T2D-induced renal injury by inhibiting oxidative stress, the NF-κB pathway, and the inflammatory response in mesangial cells. However, propionate showed only modest effects compared with the other SCFAs [58,59]. In addition, butyrate has been shown to facilitate the immunosuppressive activity and expansion of regulatory T cells (Tregs) [60] (Figure 2). Related clinical trials have revealed that Treg level in the peripheral blood is lower in patients with nephropathy than in diabetic patients without kidney damage [61]. Furthermore, fewer Treg counts were identified in DN patients and inversely correlated with the albumin-to-creatinine ratio (ACR), thereby being an indicator of renal injury [62].

SCFAs also act as signal transduction molecules to activate G-protein-coupled receptors (GPRs), including GPR41, GPR43, and GPR109A [15,63] (Figure 2). GPR41 can increase the intestinal transport rate and improve the survival and function of islet cells, which has obvious benefits for diabetes and DN [64]. The activation of GPR43 alleviates inflammation and stimulates the release of GLP-1 from L cells [65], which plays a crucial role in improving glomerular injury, tubulointerstitial fibrosis, and renal tubular epithelial inflammation and apoptosis [66]. In addition, the GLP-1/GLP-1 receptor complex has been found to partially ameliorate the renal function of early diabetes by reducing proximal renal tubule overresorption [67]. Furthermore, diabetic mice with higher fiber intake were less likely to develop DN, exhibiting less albuminuria, glomerular hypertrophy, podocyte injury, and interstitial fibrosis [15] (Figure 2). One of the most important mechanisms of this finding was the expansion of SCFA-producing bacteria, such as *Prevotella* and *Bifidobacteria* [15].

It has also been reported that SCFAs prevente diabetic mice from nephropathy, but not in the absence of GPR43 or GPR109A [15]. In

addition, SCFAs increase the production of IL-18 by activating GPR43 and GPR109A in intestinal epithelial cells (IECs) [68], and IL-18 is a crucial cytokine for repairing and maintaining epithelial integrity. Although evidence for the involvement of IL-18 in inflammatory processes has been reported, its role in barrier defense is also recognized [69,70] (Figure 2). Further studies are required to clarify the exact role of IL-18 in SCFA-mediated amelioration of DN. People with DN cannot consume foods rich in sugar and potassium, including fruits and vegetables which are fermented into SCFAs, provide a significant source of nutrients for normal colon bacteria, and are bound to affect the intestinal microbiome of DN patients. Therefore, gut microbiota dysbiosis and dietary factors could lead to abnormal SCFA production and inhibit the activation of GPRs, thus affecting the progression of DN (Figure 2).

Secondary BAs

As microbial metabolites, secondary BAs are involved in kidney diseases [16,71] (Figure 2). The activation of BA receptors, such as the nuclear hormone receptor farnesoid X receptor (FXR) and G protein-coupled receptor TGR5, plays renal-protective roles and shows prospective therapeutic potential in preventing the progression of DN [72] (Figure 2). The primary BAs are converted from precursor cholesterol in the liver and then enter the intestines where they are converted into secondary BAs by *Firmicutes* [73]. In addition, *Lactobacillus*, *Bacteroides*, and *Roseburia* also participate in the metabolic process of secondary BAs in the intestinal tract [74].

Animal studies have revealed that activation of FXR and TGR5 reduces nephritis, renal oxidative stress, and fibrosis [16] (Figure 2). For example, treatment with the FXR/TGR5 dual agonist INT-767 ameliorated albuminuria and prevented podocyte damage, mesangial dilatation, and tubulointerstitial fibrosis in diabetic mice [72], suggesting the involvement of FXR and TGR5 signaling in the progression of DN (Figure 2). Ding *et al.* [75] found that activation of TGR5 signaling induced intestinal release of GLP-1, indicating that BAs may be a promising target for DN treatment. Consistently, the TGR5-specific agonist INT-777 prevented oxidative stress and lipid accumulation in the kidneys of diabetic mice, reduced albuminuria, and improved renal podocyte injury and mesangial dilatation [76]. Furthermore, in diabetes, renal FXR and TGR5 expressions are downregulated along with their target genes which are also correlated with the severity of inflammation and renal fibrosis (Figure 2). Therefore, secondary BAs and their receptors are involved in the pathogenesis of DN and may serve as therapeutic targets.

Uremic toxins

Metabolic abnormalities in patients with DN impair protein digestion and absorption, fueling the production of protein end-products, such as p-cresol, indole, phenol and TMA, by disordered gut microbiota [28] (Figure 2). These precursors elevate hepatic production of p-cresyl sulfate (PCS), indolyl sulfate (IS), phenyl sulfate (PS) and trimethylamine N-oxide (TMAO) (Figure 2), all of which are typical uremic toxins [22,77–79]. Furthermore, *Anaerococcus hydrogenalis*, *Edwardsiella tarda* and *Escherichia fergusonii* were identified to be involved in the formation of TMA [80], while *Clostridium difficile* and *Escherichia coli* were related to the generation of p-cresol and indole, respectively [81,82]. Importantly, high levels of PCS and IS could lead to insulin resistance and renal tubulointerstitial fibrosis [83,84] (Figure 2). Moreover, due to the protein-binding toxin properties of PCS and IS, they can easily bind to albumin and cannot be removed adequately by traditional hemodialysis, leading to the deposition of these solutes in ESKD patients and possibly with increased toxicity [85]. Furthermore, Joossens *et al.* [86] demonstrated the presence of bacteria responsible for producing uremic toxins after identifying the fecal microbiota of patients with kidney disease. Specifically, *Akkermansia*, *Bacteroides*, *Blautia*, *Enterococcus*, *Dialester*, and *Ruminococcus* are related to increased uremic toxins, which seems to contradict the protective effect of *Blautia* and *Akkermansia*, as they are associated with the source of acetate and propionate [21,87].

Under normal conditions, aryl hydrocarbon receptors (AHRs) are IS receptors that regulate the function of podocytes, while the chronic activation of AHRs by high-level IS could also lead to progressive injury of podocytes and glomeruli [88] (Figure 2). *In vivo* and *in vitro* experiments confirmed that podocyte damage included cell morphology changes and increased the expressions of proinflammatory cytokines and chemokines [88]. As mentioned above, podocytes play a vital role in forming the glomerular filtration barrier and protein transport, indicating that uremic toxins may be involved in renal deterioration in patients with DN. More importantly, in a cohort of 40 patients with CKD, the researchers found that IS level is responsible for renal endothelial dysfunction, as IS level is positively related to a reduced rate of flow-mediated endothelium-dependent vasodilation. It was also found that IS restricted endothelial cell proliferation and nitric oxide production and induced oxidative stress and senescence in endothelial cells [89] (Figure 2).

In addition, elevated level of hydrogen peroxide has been reported in the plasma of patients undergoing hemodialysis compared to that in healthy individuals, and PS-treated renal tubular cells were more susceptible to oxidative stress and showed higher cell mortality induced by hydrogen peroxide than normal cells [90] (Figure 2). Meanwhile, PS caused proteinuria and podocyte injury in diabetic rats, and the level of PS was increased with the progression of diabetes but decreased in proteinuria-restricted rats [22]. In patients with microalbuminuria, the level of PS is significantly correlated with basic albuminuria and two-year progression of DN, suggesting that PS may be an early diagnostic marker and therapeutic target of DN [22] (Figure 2).

On the other hand, TMAO can be eliminated by glomerular filtration, so hemodialysis can effectively remove TMAO from systemic circulation [91]. Elevated TMAO level is associated with an increased risk of death in CKD patients [92]. Sun *et al.* [93] found that increased levels of TMAO and its precursor choline were associated with enhanced phosphorylation of SMAD3 and TGF-β signaling, thereby aggravating renal collagen deposition and tubulointerstitial fibrosis in mice fed with a high-fat diet (HFD) (Figure 2). In addition, increased TMAO level in a mouse model of diet-induced obesity was also found to be related to increased NADPH oxidase-4 and inflammatory cytokines compared with that in the control group, while supplementation with a TMA formation inhibitor ameliorated HFD-induced renal fibrosis and decreased the expressions of kidney injury molecule-1 (KIM-1) and proinflammatory cytokines in mice [93]. Xu *et al.* [94] demonstrated a significant increase in plasma TMAO level in patients with CKD, and the rise in plasma TMAO can be transferred to normal mice by transplanting

fecal microorganisms from these patients. These studies suggest that high level of TMAO might be a pathogenic mediator of CKD progression. However, direct evidence pointing to the adverse effects of TMAO on DN has thus far been absent; further studies are needed to clarify the role and mechanism of TMAO in DN progression.

Gut Microbiota-targeted Therapies for DN

From a therapeutic perspective, due to the complex metabolic disorders of DN, it is more challenging to treat the disease before it progresses to ESRD than other kidney diseases. Meanwhile, alterations in the composition and function of gut microbiota could further exacerbate these disorders. Therefore, early correct and effective treatment has important clinical significance for reversing renal function damage, delaying the progression of diseases, and optimizing the gut microbiota concurrently (Figure 3).

Dietary therapy

Experiments in animals have suggested that the benefits of intermittent fasting against a variety of metabolic diseases may be partly related to improving gut microbiota composition [95,96]. Dietary strategies rich in unsaturated fatty acids and dietary fiber are beneficial in combating metabolic endotoxemia and systemic inflammation [97]. Dietary polyphenols also boost the secretion of GLP-1 in the gut, which increases insulin level and lowers blood glucose level [98]. Furthermore, it can also facilitate the growth of certain beneficial bacteria, such as the prototypical example of *Akkermansia muciniphila* [99] with vascular protection.

Prebiotics, probiotics, and postbiotics

Prebiotics are a class of substances selectively utilized by gut microbes to benefit host health. Clinical studies have confirmed that prebiotics can ameliorate renal inflammation and fibrosis in diabetic patients, accompanied by enriching the species of *Bacteroides fragilis* and *Clostridium* and increasing the levels of SCFAs [100,101]. Furthermore, a meta-analysis of 14 randomized controlled trials showed that prebiotic intake significantly reduced circulating PCS level in patients with nephropathy [78].

Probiotics also appear to be a potential treatment for DN. Recent studies showed that prophylactic supplementation with *Lactobacillus casei Zhang* ameliorated AKI and subsequent chronic kidney fibrosis [102], while *Bifidobacterium animalis* subsp. *lactis* LKM512 attenuated inflammation and IR in mice [103]. In addition, researchers also found that in a placebo-controlled trial involving 62 patients with stage 3–5 kidney disease, *Lactobacillus casei Zhang* supplementation slowed kidney function decline with a favorable safety profile. In particular, *Oscillospira* may be a next-generation probiotic candidate, as this butyrate-producing genus has shown promising nephroprotective effects [104].

In addition to prebiotics and probiotics, postbiotics also have certain health benefits. Postbiotics include any substances released or produced by the metabolic activities of microorganisms and inactivated microbes themselves, which have beneficial effects on the host, directly or indirectly [105]. Although there is no direct evidence of postbiotics on nephroprotection, its immunomodulatory role and microbial-derived vitamins and SCFAs still suggest its potential in treating DN [106].

Prebiotics, probiotics, and postbiotics are therapeutically designed to restore the gut to its original predysmal state or a new balance, thereby eliminating or alleviating the underlying disease. However, little is known about probiotic persistence, colonization patterns, and biological host responses, and "personalized microbiome" bacteriotherapies proposed by Zmora *et al.* [107] may be a prospective solution.

Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) can reconstruct the abnormal intestinal microecology and cure intestinal microbiota disorders, such as ulcerative colitis and refractory or recurrent *Clostridium difficile* infections (CDI) [108,109]. However, direct evidence of FMT in the development of DN is still lacking. Two FMT trials showed that the microbiota of leaner donors improved insulin sensitivity in patients with metabolic syndrome, accompanied by alterations in microbiota composition, suggesting that the advantageous effects of lean FMT on glucose metabolism are related to changes in intestinal microbiota [110,111]. Another study showed that FMT from healthy donors alleviates tubulointerstitial injury by overcoming the disruption of cholesterol homeostasis, which shows the potential of FMT for the treatment of diabetes and DN [112]. Due to limited prospective safety data, the long-term effects on the host-microbial community after transplantation must be taken into account, which is also the reason why FMT is not widely used in clinical practice. More studies on the safety and efficacy of FMT are needed.

Engineering bacteria and phages

In addition to the therapies mentioned above, engineered bacteria and phages are also emerging as new therapies for treating metabolic diseases such as DN by targeting the gut microbiota. For example, daily feeding with engineered *Lactobacillus gasseri* significantly increases insulin level and improves glucose tolerance by secreting GLP-1(1–37) in diabetic rats, the mechanism of which is reprogramming the intestinal cells into glucose-responsive insulin-secreting cells by engineered bacteria [113]. Furthermore, Han *et al.* [114] observed that engineered bacteria carrying microcapsules could stably release protein drugs and reduce blood glucose within two weeks in diabetic rats, showing the great potential of engineered bacteria for the treatment of DN.

Phages are viruses that attack bacteria in a host-specific manner and thereby dominate the gut viral community. The transfer of cecal virus communities from mice with a lean phenotype into mice with an obese phenotype resulted in reduced body weight gain and normalization of glycemic parameters, and these effects might be attributable to mutual antagonism between phage and host bacteria [115]. Evidence has suggested that phages can also promote biofilm formation, conferring population-level benefits to their bacterial hosts [116]. Therefore, more attention should be paid to the therapeutic role of phages in DN.

Novel diabetic agents

GLP-1 receptor agonists

GLP-1 is a peptide hormone released by intestinal L cells, which acts by binding to the GLP-1 receptor (GLP-1R) [117]. GLP-1/GLP-1R in the human glomerular arteriole plays a protective role in maintaining GFR [118]. GLP-1 level is decreased in diabetic patients, and GLP-1R agonists can restore the function of GLP-1 [119,120]. The central agonists used in clinical practice are exenatide, liraglutide, dulaglutide, and lixisenatide (Table 2).

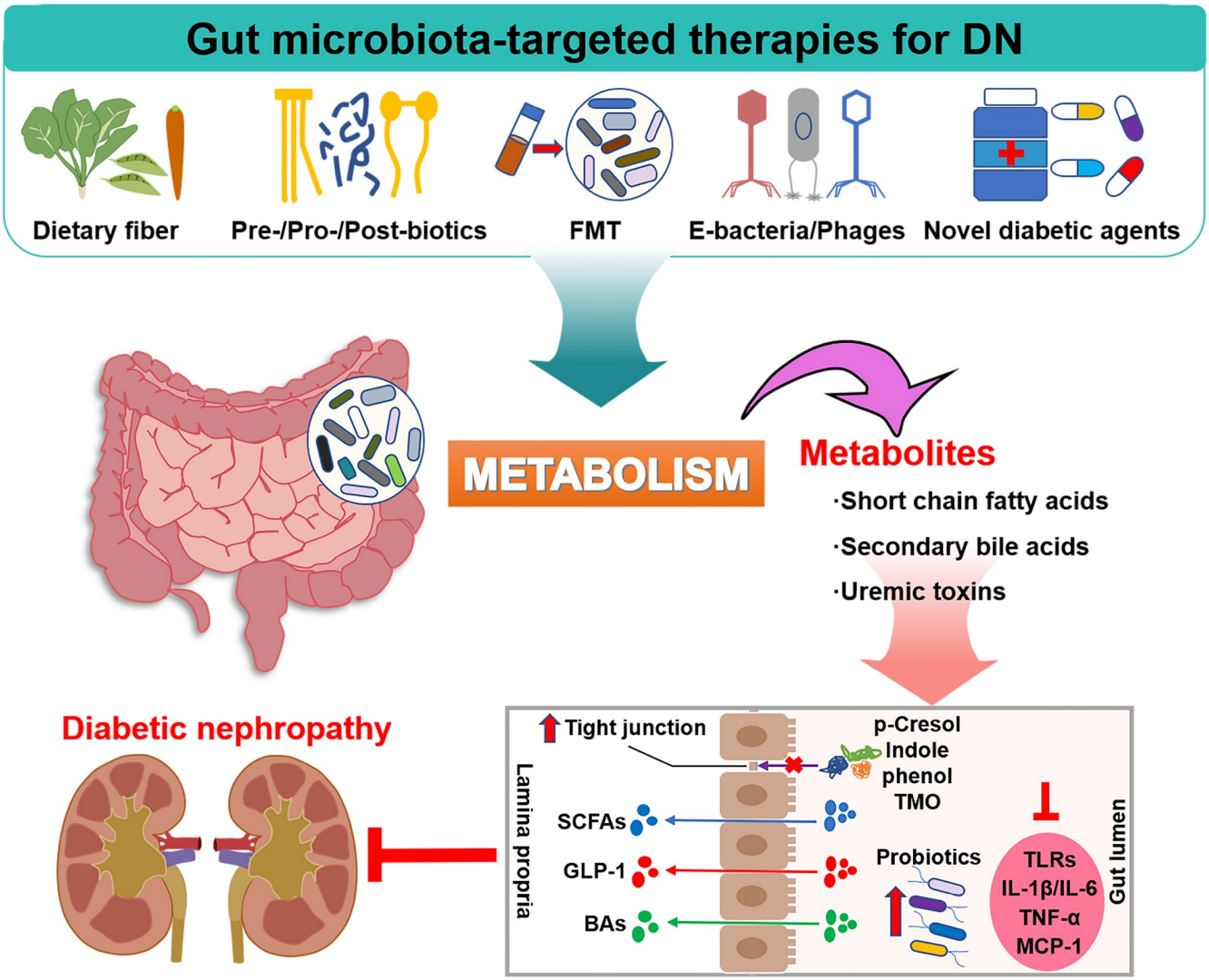

Figure 3. Gut microbiota-targeted therapies for DN Dietary fiber, prebiotic, probiotic, and postbiotic intake could increase the expression of intestinal tight junctions, improve intestinal metabolic disorders, increase the release of SCFAs and secondary BAs, and further attenuate the production of inflammatory cytokines. In addition, fecal microbiota transplantation (FMT), engineered bacteria and phages could also reshape the gut microbiota structure and exert a similar ameliorative effect on DN. Novel diabetic agents, such as glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium-dependent glucose transporter-2 (SGLT-2) inhibitors, have been found to have great potential for the clinical treatment of DN, the effects of which might be partly regulated through the gut microbiota.

As the first GLP-1R agonist, exenatide was approved by the US FDA in 2005. Animal models have shown that exenatide can reduce the excretion of oxidative stress markers and proteins in the urine and improve the histopathological changes of the kidney [121,122] (Table 2). Furthermore, exenatide alleviated fibrosis in the renal interstitium and inflammation in the glomeruli [123]. However, there has been no case about exenatide influencing gut microbiota, and renal dysfunction may affect its clearance [124].

Clinical results showed that liraglutide could improve DN symptoms and reduce the incidence of nephropathy and persistent macroalbuminuria in T2D patients [125–127] (Table 2). Results from the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial supported the addition of liraglutide to the standard of care to reduce the risk of major cardiovascular events and all-cause mortality in patients with T2D and CKD. These results appeared to apply to all patients with CKD [128]. Furthermore, liraglutide treatment seemed to reverse microbiota dysbiosis in mice with disease states, with decreased Actinobacteria and Desulfovibrio and increased S24-7 [129,130] (Table 2). It is worth mentioning that liraglutide also increases the relative abundance of *Akkermansia* in *db*/*db* mice [129], a new type of probiotic in the gut, suggesting the possibility of microbiota-modulating effects of liraglutide in the treatment of DN.

Results from dulaglutide and renal outcomes in T2D, an exploratory analysis of the Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND) trial, showed that diabetic patients treated with dulaglutide had a lower incidence of new-onset large albuminuria and a sustained decline in eGFR than the placebo group [131] (Table 2). Dulaglutide also reduced the incidence of ischemic stroke and non-fatal stroke or all-cause death in patients with T2D compared with placebo [132]. In addition, an increase in the abundance of *Akkermansia* was found after

Table 2. Effects of diabetic drugs on gut microbiota and renal outcomes

Agent	Drug	Effect on gut microbiota			Effect on renal outcome	Reference
		Phylum level	Family level	Genus/species level		
GLP-1 receptor agonists	Exenatide	Unknown	Unknown	Unknown	Reduce albuminuria and pathological renal injury	121,122
	Liraglutide	*Bacteroides*↑, *Verrucomicrobia*↑, *Proteobacteria*↓, *Actinobacteria*↓	*Rikenellaceae*↑, *S24-7*↑, *Erysipelotrichaceae*↑, *Lachnospiraceae*↓, *Peptostreptococcacea*↓	*Akkermansia*↑, *Romboutsia*↑, *Anaerotruncus*↓, *Klebsiella*↓, *Lachnospiraceae_UCG-001*↓, *Lachnospiraceae_N-K4A136_group*↓, *Ruminiclostridium*↓, *Desulfovibrio*↓	Reduce the incidence of nephropathy and macroalbuminuria	125,127,129,130
	Dulaglutide	*Bacteroides*↑, *Firmicutes*↓	Unknown	*Aerococcus*↑, *Akkermansia*↑, *Bacteroides*↑, *Barnesiella*↑, *Ruminococcus*↑, *Oscillibacter*↑, *Coprobacillus*↓	Lower the incidence in new-onset large albuminuria and sustained decline of eGFR	131,133
	Lixisenatide	Unknown	Unknown	Unknown	Improve UACR	134,135
DPP-4 inhibitors	Linagliptin	*Bacteroides*↑, *Actinobacteria*↓, *Proteobacteria*↓	Unknown	Unknown	Reduce proteinuria and improve renal injury	140,142,143
	Alogliptin	Unknown	Unknown	Unknown	Improve UACR and maintain eGFR	144
	Saxagliptin	*Firmicutes*↑, *Bacteroides*↓	*Erysipelotrichaceae*↑, *Bacteroidaceae*↓	*Lactobacillus*↑, *Allobaculum*↑, *Turicibacter*↑, *Prevotella*↓	Improve UACR	147,148
	Sitagliptin	*Bacteroides*↑, *Proteobacteria*↑, *Actinobacteria*↑, *Firmicutes*↓, *Tenericutes*↓	*Ruminococcaceae*↑	*Roseburia*↑, *Bifidobacterium*↑, *Blautia*↓	Reduce urinary albumin levels	150,151
SGLT-2 intibitors	Canagliflozin	*Actinobacteria*↓, *TM-7*↓	Unknown	*Alistipes*↑, *Alloprevotella*↑, *Olsenella*↑, *Oscillospira*↓, *Bifidobacterium*↓, *Helicobacter*↓, *Mucispirillum*↓	Reduce plasma uremic toxins and lower UACR	155,157,158
	Dapagliflozin	*Firmicutes*↑, *Proteobacteria,*↑ *Bacteroides*↓, *Actinobacteria*↓	*Desulfovibrionaceae*↑, *Lactobacillaceae*↓	*Oscillospira*↓, *Mucispirillum*↓, *Barnesiella*↓	Prevent progression of kidney disease	160 – 163
	Empagliflozin	*Bacteroides*↑, *Firmicutes*↓	Unknown	*Bacteroides*↑, *Bifidobacterium*↑, *Parabacteroides*↑	Reduce the risk of nephropathy, proteinuria and serum creatinine	133,164,165
	Ertugliflozin	Unknown	Unknown	Unknown	Reduce the risk of renal composite end-point and preserve eGFR and UACR	167,168

dulaglutide treatment in mice, and coupled with its promoting effects on GLP-1 secretion, *Akkermansia* might be a potential target for GLP-1 receptor agonists [117,133] (Table 2).

The Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 (Lixisenatide) (ELIXA) trial revealed that lixisenatide slowed the progression of UACR in patients with large proteinuria and reduced the likelihood of significant proteinuria without increasing cardiovascular risk [134,135] (Table 2). However, no such change of an increased abundance of *Akkermansia* has been found in lixisenatide yet. In summary, GLP-1 receptor agonists might prevent and improve DN symptoms in mice and patients, possibly through the gut microbiota. However, more direct evidence linking the cause and effect of the microbiota in DN is urgently needed.

DPP-4 inhibitors

Under physiological conditions, GLP-1 has a half-life of approximately two minutes and is rapidly degraded by DPP-4 [136]. DPP-4 inhibitors can inhibit the activity of DPP-4 and increase the utilization of GLP-1. In addition, DPP-4 inhibitors were found to alleviate inflammation and oxidative stress in the kidneys of diabetic patients to delay glomerulosclerosis [137–139]. The

representative drugs of DPP-4 inhibitors include linagliptin, alogliptin, saxagliptin, and sitagliptin (Table 2).

Tanaka *et al.* [140] found that linagliptin restrained the inflammatory response induced by free fatty acid (FFA)-binding albumin in proximal tubule cells and exhibited a significantly ameliorative effect on kidney injury in mice. In an earlier clinical trial, linagliptin also reduced proteinuria in adults with T2D [141]. However, linagliptin cannot reduce albuminuria but effectively improves glycemic control in the early stage of DN, indicating its primary hypoglycemic function and specific renal repair ability [142]. A decrease in the relative abundance of *Actinobacteria* was also observed after linagliptin treatment [143] (Table 2).

In a long-term follow-up of 36 diabetic patients with kidney disease, alogliptin reversed the steady decline in eGFR and showed a downwards trend in UACR. However, this study did not provide evidence that alogliptin could improve renal function due to the sample size limitation [144] (Table 2). In addition, alogliptin appeared to be more effective when combined with other drugs [145,146], although it has not been reported to affect the gut microbiota.

Saxagliptin treatment could improve UACR without affecting eGFR in patients with T2D who were followed for a median of 2.1 years on renal outcomes [147]. In addition, saxagliptin increased the F/B ratio and the relative abundance of *Lactobacillus*; simultaneously, the respective rise and fall of *Allobaculum* and *Prevotella* appeared to be at odds with therapeutic efficacy [148] (Table 2).

Diabetic patients treated with sitagliptin showed a significant decrease in glycosylated hemoglobin and inflammation-related cytokines, suggesting a potent and rapid anti-inflammatory effect of sitagliptin [149]. A randomized clinical trial showed that sitagliptin improved glucose and chylomicron metabolism and reduced urinary albumin level in T2D patients [150] (Table 2). In addition to its renal protective effects, sitagliptin also increased the levels of certain probiotics, *Bifidobacterium*, and butyrate-producing bacteria, *Roseburia*, even though another study reported that sitagliptin did not affect gut microbiota [151,152] (Table 2). Therefore, these DPP-4 inhibitors showed excellent hyperglycemic and urinary albumin-lowering effects. However, more subsequent clinical trials are expected to confirm whether they have better renal protection in the progression of DN through gut microbiota.

SGLT-2 inhibitors

SGLT-2 is found in the renal proximal convoluted tubules and mainly mediates the process of renal glucose reabsorption [153]. SGLT-2 inhibitors primarily act on the SGLT-2 receptor in the proximal tubule to increase glucose excretion to the urine to reduce blood glucose level and improve glomerular hyperperfusion and hyperfiltration, subsequently restoring renal function [154]. Currently listed SGLT-2 inhibitors include canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin (Table 2).

In a randomized, double-blind trial, the relative risk of doubling creatinine levels or mortality from renal causes was 34% lower in the canagliflozin-treated group with a reduced relative risk of developing ESRD, demonstrating its clinical efficacy and safety in renal disease protection [155] (Table 2). Consistent with these results, canagliflozin reduced the risk of cardiovascular and renal events in patients with T2D and proteinuria [156]. Similarly, a decrease in *Actinobacteria* was observed after canagliflozin treatment, along with a decline in *TM-7* in mice. Furthermore, a reduction in the relative abundance of the opportunistic pathogen *Mucispirillum* was observed. *Oscillospira* also showed a decrease after canagliflozin intervention [157,158] (Table 2).

In a randomized trial with a sustained reduction of at least 50% in eGFR, ESRD, or death from renal or cardiovascular causes as the primary outcome, patients with kidney disease in the dapagliflozin-treated group had a significantly lower compound risk for renal endpoints [159]. In addition, in the DECLARE-TIMI 58 trial, dapagliflozin preserved renal function in most patients [160], which is undoubtedly a boon for DN patients (Table 2). Among the changes in the gut microbiota, the increase of *Firmicutes* and *Proteobacteria* and the decrease of *Actinobacteria* were first observed at the phylum level after dapagliflozin intervention [161]. In addition, *Oscillospira* and *Mucispirillum* mentioned above were also declined [162,163], and these two bacteria may act as targets of SGLT-2 inhibitors (Table 2).

Empagliflozin decreased UACR and urinary albumin level in T2D patients with complicated cardiovascular disease after short-/long-term therapy [164,165] (Table 2). Further findings of EMPA-REG OUTCOME supported that empagliflozin lowered the risk of clinically relevant renal events and might delay the progression of DN [166]. In terms of gut microbiota, it was found that the relative abundance of *Bifidobacterium* was increased after empagliflozin treatment in mice [133].

Analyses from the Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes (VERTIS CV) trial showed that ertugliflozin led to a lower incidence of the exploratory renal composite outcome of a sustained reduction in eGFR, chronic renal dialysis/transplantation, or renal death compared with the placebo control [167]. In addition, both UACR and eGFR tended to be close to their baselines after ertugliflozin treatment [167,168] (Table 2). Therefore, based on the above clinical data, the nephroprotective effects of SGLT-2 have been gradually revealed. Its impact in DN treatment is worthy of expectation, especially in its association with gut microbes, even though ertugliflozin has not been reported to affect the gut microbiota.

In addition to the novel diabetes agents mentioned above, more and more effective DN therapy strategies are being developed [169], targeting multiple metabolic pathways including inhibitors of protein kinase C (PKC), advanced glycated end product (AGE), endothelin receptor (ETR), and transforming growth factor-β (TGF-β), and so on, which have shown promising prospects in the treatment of DN. More recently, the concept of machine learning (ML) has been proposed to describe and predict drug-microbiome interactions at the level of individual patient [170], which may become the mainstream treatment for DN and even ESRD in the future.

Conclusion and Prospect

Gut microbiota dysbiosis is closely related to metabolic diseases such as DN. Intestinal dysbacteriosis and kidney damage lead to loss of beneficial bacterial strains, accumulation of large amounts of uremic toxins, and increased incidence of UTIs, all of which contribute to the progression of DN. Gut microbiota-based therapy might be a promising strategy for preventing and treating DN in the future. Changes in dietary structure contribute to the improvement of intestinal microbiota dysbiosis. Microbiota transplantation is also expected to play a role in restoring the microflora ecology of DN under safe and standardized conditions. In addition, burgeoning

hypoglycemic drugs, such as GLP-1 receptor agonists, DPP-4 inhibitors, and SGLT-2 inhibitors targeting the gut microbiota, have shown reliable therapeutic effects on the renoprotection and modification of gut microbiota. However, most of the current data are limited to rodent models, and more reliable clinical trials are needed to elucidate pivotal pathways and specific strains in the pathogenesis of DN.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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