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The crosstalk of gut microbiota and chronic kidney disease: role of inflammation, proteinuria, hypertension, and diabetes mellitus

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Abstract

Chronic kidney disease (CKD) has been shown to result in profound changes in the composition and functions of the gut microbial flora which by disrupting intestinal epithelial barrier and generating toxic by-products contributes to systemic inflammation and the associated complications. On the other hand, emerging evidence points to the role of the gut microbiota in the development and progression of CKD by provoking inflammation, proteinuria, hypertension, and diabetes. These observations demonstrate the causal interconnection between the gut microbial dysbiosis and CKD. The gut microbiota closely interacts with the inflammatory, renal, cardiovascular, and endocrine systems via metabolic, humoral, and neural signaling pathways, events which can lead to chronic systemic inflammation, proteinuria, hypertension, diabetes, and kidney disease. Given the established role of the gut microbiota in the development and progression of CKD and its complications, favorable modification of the composition and function of the gut microbiome represents an appealing therapeutic target for prevention and treatment of CKD. This review provides an overview of the role of the gut microbial dysbiosis in the pathogenesis of the common causes of CKD including hypertension, diabetes, and proteinuria as well as progression of CKD.

Keywords Gut microbiota · Chronic kidney disease · Inflammation · Hypertension · Proteinuria · Diabetes

Introduction

Gut microbiota, a highly diverse bacterial population [1] consisting of approximately 10^{14} bacteria [2], has recently drawn attention as a central player in the development of many chronic diseases, including chronic kidney disease (CKD). Alterations in the gut microbiota are associated with the development of proteinuria [3], inflammation, type 2 diabetes [4], type 1 diabetes [5], and hypertension [6]. The gut microbiota is in a bidirectional interaction with the kidneys and deterioration in this relationship results in CKD development [7]. Therefore, gut microbiota can be considered an important player in the pathogenesis of CKD directly and indirectly by influencing the development of diabetes, hypertension, and proteinuria. For this reason, "engineering" the gut microbiota via lifestyle modifications and therapeutic interventions represents a potential target for prevention and treatment of CKD.

Gut microbiota, inflammation, and chronic kidney disease

CKD is associated with chronic systemic inflammation [8] which is a cornerstone in the development and progression of CKD [9]. Previous studies have identified gut microbiota as one of the important mediators of systemic inflammation [7]. In fact, kidney diseases such as tubulointerstitial nephritis, nephrolithiasis, amyloidosis, and glomerulonephritis

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commonly occur in patients with inflammatory bowel diseases (IBD) [10]. Interestingly, CKD and IBD share some similarities in the composition of the gut microbiome. Species from *Bacteroidetes* and *Enterobacteriaceae/Proteobacteria* genres are increased while other genera such as *Prevotella* and *Lactobacilli* are decreased [11, 12]. Therefore, gut dysbiosis could contribute to the pathogenesis of systemic inflammation in CKD and IBD.

The normal gut microbiota can protect the kidney whereas gut dysbiosis can facilitate CKD development [13]. The gut dysbiosis in CKD includes an increase in the species from *Enterobacteriaceae* and *Pseudomonadaceae* genera of the phylum Proteobacteria, *Bacteroidaceae*, and *Clostridiaceae*; and a decrease in species from *Lactobacillaceae, Prevotellaceae*, and *Bifidobacteriaceae* [12]. Strikingly, the species that are expanded in CKD are generally capable of inducing local and systemic inflammation directly and indirectly. For example, Proteobacteria, the gram-negative phylum containing both *Enterobacteriaceae* and *Proteobacteriaceae* can induce inflammatory response by: compromising the gut mucosal barrier function (increasing gut's mucus permeability [14]), increasing intestinal T helper 17 (Th17) cell to T regulatory (Treg) cell ratio [15], and by enabling translocation of lipopolysaccharide (LPS) and gut bacterial components to the systemic circulation [16].

In addition, the microbial species that are increased in CKD produce pro-inflammatory substances including p-cresyl sulfate, indoxyl sulfate, trimethylamine *N*-oxide (TMAO) [17, 18], bile acids deoxycholic acid (DCA) and lithocholic acid (LCA) [19]; at the same time, acetylcholine (Ach) which is an anti-inflammatory neurotransmitter with renal protective properties is degraded [20].

Changes in microbiota also involve depletion of protective microbial species including bacteria that fortify the gut barrier function [21]; bacteria that produce anti-inflammatory and cytoprotective substances such as short-chain fatty acids (SCFA) [18], γ-aminobutyric acid (GABA) [22], ACh [20], nitric oxide (NO) [23], chenodeoxycholic acid (CDCA), and ursodeoxycholic acid (UDCA) [19], vitamin B complex [24], peptide YY (PYY), and glucagon-like peptide 1 and 2 [25]; and finally microbial species capable of stimulating the anti-inflammatory vagal system [26] and suppressing the mostly pro-inflammatory sympathetic activity by means of reducing pain and anxiety [26].

Based on the above observations the CKD-associated intestinal epithelial barrier dysfunction [12], accumulation of the gut-derived uremic toxins [17, 18], reduction of group B vitamins [24], NO deficiency, increased sympathetic and depressed vagal activity may be, in part, mediated by the gut microbiota dysbiosis [26].

Inflammation plays a central role in the pathogenesis of CKD directly by inflicting renal injury and indirectly by promoting the development and progression of the disorders that cause CKD including diabetes, hypertension, and proteinuria. Considering the role of gut dysbiosis in promoting systemic inflammation, its presence can contribute to the development and progression of CKD and its major risk factors. The relationship between gut microbiota/inflammation and the renal system is not one-sided. As the renal function deteriorates, several changes occur in renal handling of water, minerals, metabolic waste products and toxins as well as renal endocrine function. Renal failure results in fluid overload, accumulation of uremic toxins and waste products, hyperphosphatemia, and electrolyte disorders which work in concert to promote changes in gut microbiota by several mechanisms.

Taken together, the emerging data demonstrate the causal interaction between the gut microbial dysbiosis and kidney disease in which by promoting chronic inflammation gut dysbiosis causes CKD, and by modifying the biochemical and biophysical milieu of the gut, CKD transforms the gut microbiome to dysbiotic state, thereby creating a vicious cycle [27].

Gut microbiota, proteinuria, and chronic kidney disease

Proteinuria is a strong risk factor for development and progression of CKD as proteinuric diseases such as treatment-resistant nephrotic syndrome can culminate in CKD [28]. Gut microbial dysbiosis is associated with a number of proteinuric renal disorders such as IgA nephropathy and lupus nephritis [29]. Via controlling Treg activity, the gut microbiota can affect the development of idiopathic nephrotic syndrome since enhanced Treg activity has been shown to alleviate it [15]. In addition, development of renal amyloidosis, could be supported by the gut dysbiosis-induced chronic inflammation leading to production of serum amyloid A (SAA) which is up regulated in chronic inflammatory conditions [30]. Furthermore, gut microbiota can contribute to the development of hypertension [6] and diabetes [4, 5]; which can both cause proteinuria via renal arterial hyalinosis and diabetic nephropathy, respectively. In summary, by several mechanisms the gut microbial dysbiosis can contribute to the development of proteinuria.

The gut microbiota displays some changes in a variety of diseases which can lead to proteinuric kidney disease. The most striking change in the gut flora of patients with the proteinuric diseases listed in Table 1 is the decline in the level of species from the Lactobacillus and Bifidobacterium genera. In fact, these two genera are among the most well-known probiotics with numerous useful functions such as protection of the gut barrier structure [21], productions of SCFA [18], NO [31], vitamin B [24], Ach, and GABA [22]; and SCFA-mediated production of incretins

Table 1 The changes in the gut microbiota in CKD and in various nephropathies

	Increased genera	Decreased genera
CKD	Enterobacteriacece, Clostridia, Bacteroidia, Pseudomonadaceae	Bifidobacteriaceae, Lactobacillaceae, Prevotellaceae
IgA nephropathy	Enterobacteriaceae, Sutterellaceae, Ruminococcaceae, Streptococcaceae, Lachnospiraceae, Eubacteriaceae	Clostridium, Lactobacillus, Enterococcus, Bifidobacterium
Lupus nephritis		Lactobacillus [29]
Hypertensive nephropathy[a]	Prevotella, Klebsiella, Porphyromonas, Actinomyces, Streptococcus, Turicibacter, S24-7, Veillonellaceae, Lactococcus, Coprobacillus	Faecalibacterium, Oscillibacter, Roseburia, Bifidobacterium, Coprococcus, Butyrivibrio, Pseudobutyrivibrio, Ruminococcaceae
Diabetic nephropathy[a]	Type 1 DM: Bacteroides, Blautia, Rikenellaceae, Ruminococcus, Streptococcus, *Clostridium perfringens*, Veillonella, Fusobacteria, (Leptotrichia) Type 2 DM: Escherichia, Prevotella, *Clostridium bolteae, Clostridium symbiosum, Clostridium ramosum, Clostridium hathewayi*, Betaproteobacteria, Desulfovibrio	Type 1 DM: Lactobacillus, Bifidobacterium, Prevotella, Staphylococcus, Lachnospiraceae, Veillonellaceae, *Coprococcus eutactus, Dialister invisus, Roseburia faecis, Faecalibacterium prausnitzii, Clostridium clostridioforme, Blautia coccoides*, Pseudobutyrivibrio, Akkermansia muciniphila[b] Type 2 DM: Bifidobacterium, *Eubacterium rectale*, Faecalibacterium, *Roseburia intestinalis*, Clostridiales, Lactobacillus, *Akkermansia muciniphila*[b] (Verrucomicrobiaceae), Streptococcus

[a]Since hypertension and diabetes are important causes of renal disease, the gut dysbiosis seen in hypertension and diabetes could be contributors for the development of hypertensive and diabetic nephropathy

[b]Akkermansia was found to be more enriched in patients with type 2 diabetes and multiple type 1 diabetes mellitus (DM)-related antibodies than a single antibody

glucagon-like peptide-1 (GLP-1), GLP-2, and PYY [25]. The above-mentioned functions render these species "anti-inflammatory bacteria" [24] by protecting the host from chronic inflammatory disorders such as autoimmune diseases, hypertension, and diabetes, conditions that can cause proteinuric nephropathy. On the other hand, in most of the diseases mentioned above, certain genera from the Proteobacteria phylum have been reported to be enriched. Since Proteobacteria can induce inflammation by disrupting gut barrier function [14–16] and producing pro-inflammatory substances, uremic toxins and serotonin [17], increased Proteobacteria population may contribute to the pathogenesis of a variety of chronic inflammatory diseases that lead to proteinuric nephropathy. However, the patterns of gut dysbiosis vary in different diseases; for example species from the genus Prevotella are increased in hypertension [32] and type 2 DM [33] but reduced in CKD [12]. Likewise, the levels of some genera such as Prevotella and Clostridium display different changes in these diseases. For instance, although Prevotella can produce SCFA [18] and therefore increase incretin secretion [25] to reduce inflammatory tone and insulin resistance, as a gram-negative species, it can induce inflammatory response via LPS [34]. Moreover, its enrichment in the gut flora is associated with an elevation of trimethylamine *N*-oxide (TMAO) [35] and stearic acid, the latter being an important hypertension-related metabolite [32]. Similarly, Clostridium which can produce SCFA and increase the anti-inflammatory Treg activity [36] can also produce uremic toxins [18]. Therefore, some bacteria can

potentially have both beneficial and harmful effects on the host and thus depending on which effects are pronounced, they can exert either protective or deleterious impacts on the host. Also, as listed in Table 1, composition of the gut flora is different in different proteinuric diseases pointing to the underlying conditions, as opposed to proteinuria per se, in shaping the structure of the gut microbiome. Taken together, composition of the gut microbiota is closely associated with the renal diseases that cause proteinuria.

Considering that the pro-inflammatory uremic toxins also directly damage the kidneys [37, 38] and promote hypertension [39] and insulin resistance [40], it is conceivable that hypoalbuminemia may intensify the toxic effects of the protein-bound uremic toxins produced by the gut flora. Also, with the exception of indole [41], the integrity of the gut mucosa could be compromised by the pro-inflammatory protein-bound uremic toxins especially in their free forms which enable them to accumulate in various tissues including the gut mucosa. This is exemplified by *p*-cresol which has detrimental effects on the human colonic epithelium [42]. Thus, by raising the free fraction of these toxins, heavy proteinuria can amplify their damaging effect on various tissues including the gut mucosal barrier. Lastly, plasma proteins act as the carriers of several hormones, and the plasma level of the protein-bound hormones decline in parallel with the plasma protein levels in proteinuric diseases. Therefore, losses of the protein-bound thyroid hormones in proteinuric diseases can promote the development of CKD as well as its risk factors and disruption of the gut mucosal barrier function (Table 2).

Table 2 The relationship between gut microbiota, proteinuria, and chronic kidney disease

- Via controlling Treg activity gut microbiota can affect the development of idiopathic nephrotic syndrome [Ref. 15]
- Renal amyloidosis, could be supported by the gut dysbiosis-induced chronic inflammation leading to production of serum amyloid A (SAA) [Ref. 30]
- In proteinuric diseases, there is decline in the level of beneficial species from the Lactobacillus and Bifidobacterium genera which protects epithelial barrier function [Ref. 21]
- Gut microbial dysbiosis is associated with a number of proteinuric renal disorders such as IgA nephropathy and lupus nephritis [Ref. 29]
- Probiotic treatment may decrease protein excretion and attenuated systemic inflammation as evaluated by serum lipopolysaccharide, interleukin-6, and C-reactive protein levels in rats by 5/6 nephrectomy (Nx rats). Histologically, renal sclerosis in Nx rats was restored by Lact treatment. A reduction in the expression of tight junction proteins and the Toll-like receptor 2 (TLR2), a putative Lact receptor, in the colons of Nx rats were mitigated by Lactobacillus [Ref. 3]

Gut microbiota and hypertension

Another important risk factor for CKD is hypertension which results in renal arteriolar sclerosis and nephrosclerosis. Mounting evidence has shown that arterial blood pressure can be affected by the gut microbiota [6]. In fact, a causal relationship between gut dysbiosis and hypertension has been implied by studies in which transplantation of fecal material from hypertensive patients or rats to normotensive mice or rats resulted in elevation of blood pressure in normotensive animals [32, 43]. Therefore, hypertension can be another pathway through which gut dysbiosis can promote CKD development.

In order to explore the potential association of hypertension with the gut microbiota several studies have compared hypertensive patients and animals with their normotensive counterparts. In general the overall diversity of the gut flora is reduced [32] and the Firmicutes to Bacteroidetes ratio is increased in hypertension [44]. Specifically, Prevotella, Klebsiella, Desulfovibrio, Porphyromonas, Actinomyces, Streptococcus, Turicibacter, Veillonellaceae, Lactococcus, Coprobacillus [43] were found to be increased while Faecalibcterium, Oscillibacter, Roseburia, Bifidobacterium, Coprococcus, Clostridium, Butyrivibrio, Pseudobutyrivibrio, and Ruminococcaceae [43] were decreased in hypertensive subjects. The observed changes in the composition of the gut microbiota can, in part, account for the hypertension-associated increase gut mucosal permeability [45] via: a—reduction of Clostridium, which by increasing Treg activity in colonic mucosa [15] which reduces inflammation and protects gut mucosal integrity, b—expansion of some species from Proteobacteria (Klebsiella, Desulfovibrio), which can intensify gut mucosal barrier dysfunction by amplifying inflammatory profile and damaging colonocytes with H_2S [34]. Another noteworthy change in the hypertensive gut microbiota is the increase in gram-negative species such as Prevotella, Klebsiella, Desulfovibrio, and Veillonella which can contribute to the pathogenesis of hypertension by promoting LPS-mediated chronic inflammation [34]. On the other hand, Bifidobacteria which suppress the intestinal LPS levels and protect the gut barrier function [32], are decreased in hypertension [46]. In addition, the gut microbiota in hypertensive subjects displays a trend towards lower SCFA and higher lactate-producing phenotypes [6] which can contribute to elevation of blood pressure since SCFAs have anti-hypertensive properties [47] whereas lactate is associated with hypertension [48]. SCFAs are important anti-hypertensive metabolites not only for being anti-inflammatory [49], but also by stimulating release of the incretin GLP-1 [25], which has potential anti-hypertensive properties through its vasodilatory effects [50]. Furthermore, Bifidobacteria species which produce the potent vasodilator, NO, [23], are significantly depleted in the gut flora of hypertensive subjects [6]. Moreover, the reduction of Bifidobacteria which produce the anti-hypertensive neurotransmitter, GABA [22] and expansion of the Proteobacteria which produce the pro-hypertensive neurotransmitters noradrenalin (NE) and serotonin that contribute to elevation of blood pressure in hypertensive population. Lastly, gut dysbiosis can contribute to hypertension via increased sympathetic activity in response to the leaky gut-mediated release of inflammatory mediators [15] and diminished production of sympathetic inhibitor GABA due to the depletion of Bifidobacteria [22]. Therefore, the gut dysbiosis contributes to the development of hypertension via inflammatory, metabolic, endocrine, and neurological pathways.

Finally, by damaging vessels and reducing collateral formation the combination of diabetes and hypertension can work in concert to compromise tissue perfusion [51]. The reduction of the intestinal mucosal perfusion can have deleterious effects on the gut mucosal barrier and microbiota, as seen in intestinal ischemia–reperfusion injury in which the gut mucosal integrity is disrupted [52] and gut dysbiosis occurs with expansion of Escherichia and the decline of Lactobacilli and Lachnospiraceae [53], increased bacterial adhesiveness and virulence. Taken together, hypertension contributes to the development of CKD and CKD results in development and intensification of hypertension; events which work in concert to induce gut microbial dysbiosis and impair epithelial barrier structure and function (Table 3).

Table 3 The relationship between gut microbiota and hypertension

- Mounting evidence has shown that arterial blood pressure can be affected by the gut microbiota due to lower short-chain fatty acids and higher lactate-producing phenotypes [Ref. 6]
- Studies showed that transplantation of fecal material from hypertensive patients or rats to normotensive mice or rats resulted in elevation of blood pressure in normotensive animals [Refs. 32, 33]
- Firmicutes to Bacteroidetes ratio is increased in hypertension [Ref. 44]
- Prevotella, Klebsiella, Desulfovibrio, Porphyromonas, Actinomyces, Streptococcus, Turicibacter, Veillonellaceae, Lactococcus, Coprobacillus are usually increased while Faecalibcterium, Oscillibacter, Roseburia, Bifidobacterium, Coprococcus, Clostridium, Butyrivibrio, Pseudobutyrivibrio, and Ruminococcaceae were decreased in hypertensive subjects [Ref. 43]
- The observed changes in the composition of the gut microbiata can, in part, account for the hypertension-associated increase gut mucosal permeability via: a- reduction of Clostridium, which by increasing Treg activity in colonic mucosa [Refs. 15, 45]
- Gut dysbiosis can contribute to hypertension via increased sympathetic activity in response to the leaky gut-mediated release of inflammatory mediators [Ref. 15]

Gut microbiota and diabetes

One of the serious complications of diabetes is diabetic nephropathy which is the most common cause of CKD worldwide. Growing evidence suggests that the gut microbiota is an important determinant of the development of diabetes. Actually, as supported by fecal transplantation studies, alterations of the gut microbiota directly affect the course of both type 1 and type 2 diabetes development [54, 55]. Therefore, understanding of the role of gut microbiota in the pathogenesis of diabetes is essential in developing better strategies for the management of diabetes and its complications including CKD.

The gut dysbiosis seen in type 1 and type 2 diabetes display some differences, yet there are important disturbances in the gut microbiota and of mucosa which are shared by both diseases. To begin with, the gut mucosal barrier function is compromised in both type 1 and type 2 diabetes [56, 57]. Interestingly, the abundance of many microbial genera related to the gut mucosal barrier function is changed in these diseases such that Lactobacilli, Bifidobacteria, Pseudobutyrivibrio, Roseburia, and Faecalibacterium are reduced while *Clostridium perfringens*, Bacteroides spp., Prevotella, Betaproteobacteria, and Desulfovibrio are enriched [5, 33]. Probiotic bacteria such as Lactobacilli and Bifidobacteria which are depressed in diabetes can strengthen the gut mucosal barrier function by stabilizing the tight junctions between the intestinal epithelial cells and promoting the secretions of mucus, secretory immunoglobulin A (sIgA), the antimicrobial protein β-defensin [21], and GLP-2 [18], an incretin with trophic effects on the gut mucosa [57]. In addition, the other genera that are decreased in diabetes either directly (Pseudobutyrivibrio [58], Roseburia, Faecalibacterium [59] or indirectly (Lactobacilli, Bifidobacteria [60]) produce butyrate, a SCFA which contributes to the gut barrier integrity by "feeding" the colonocytes [61], promoting tight junction assembly [62], and enhancing mucus production [63]. On the other hand, the species enriched in diabetes are mucolytic

bacteria such as *C. perfringens* and species from Desulfovibrio, Bacteroides [64], and Prevotella [65]. Clostridium perfringens damages the gut mucosa via its toxins [66] and as a member of the Proteobacteria phylum, Betaproteobacteria may increase mucus barrier permeability [14]. Gut barrier dysfunction is an important factor in the development of type 1 and type 2 diabetes by enabling the leakage of pro-inflammatory bacterial products such as LPS, which cause insulin resistance [67] and accelerate progression of kidney disease in diabetic patients [68]. Also, the gut dysbiosis seen in type 1 diabetes includes an increase in population of Leptotrichia goodfellowii [69], which possesses an antigen that provokes the CD8$^+$ T cells to attack pancreatic islets through molecular mimicry [69] and accelerate development of type 1 diabetes by increasing the exposure of the CD8$^+$T cells to the aforementioned antigen. In addition, the gut microbial dysbiosis seen in diabetes can affect Th cell differentiation. For instance some species from Lactobacilli, Bifidobacterium, Clostridium spp. [70], *Bacteroides fragilis* [71], and butyrate-producing bacteria [72] can promote Treg differentiation; and Lactobacilli and Bifidobacteria may be able to induce mucosal-associated invariant T (MAIT) cells via vitamin B production [73–75]. Treg and MAIT cells have known anti-inflammatory properties [76]; in fact, Treg cells are reduced in both type 1 and type 2 diabetes [77, 78]. The reduction in the Treg activity in diabetic patients can be, in part, mediated by the decrease in population of most of the Treg-supporter species in the gut flora. Besides its interactions with the gut barrier and the immune system, the gut microbiota can affect the course of the development and progression of diabetes by altering the gut endocrine function and the composition of metabolites produced by microbial flora. Firstly, the SCFAs, which are produced by some important probiotic bacteria such as Lactobacilli, Bifidobacteria, and the butyrate-producing species [18, 31, 58, 59] can protect against type 1 diabetes [79] possibly through inducing apoptosis in the macrophages infiltrating the pancreatic islets [80]. In addition they can alleviate

progression of type 2 diabetes by directly inducing pancreatic insulin secretion [81] and reducing insulin resistance [82] while increasing β-cell survival [83]. Also, SCFAs induce the secretion of GLP-1 [84], which can improve blood glucose levels in type 1 diabetes [85], and decrease insulin resistance [86] while increasing insulin secretion [87] in type 2 diabetes. Thus, the extensively documented depletion of the SCFA-producing species in both type 1 and type 2 diabetes [33] results in the loss of the aforementioned beneficial effects of the SCFAs and incretins. In addition, Lactobacilli and Bifidobacteria can produce several other metabolites and neurotransmitters that reduce insulin resistance such as CDCA [19], group B vitamins [73], GABA [22], ACh [20], and NO [23], thereby exerting beneficial effects especially on type 2 diabetes. Also, having anti-inflammatory [88] and immunomodulatory properties [89], both GABA [89] and riboflavin [88] can support β cell survival; being especially valuable for type 1 diabetes. In fact, a GABA-producing Lactobacillus strain has been shown to reduce hyperglycemia in rats with streptozotocin-induced diabetes [90]. Moreover, the vascular and other complications of diabetes can be alleviated by NO [91] and group B vitamins [92], even though not all studies confirm the vasoprotective effects of folate in diabetic patients [93]. The farnesoid X receptor (FXR) has been shown to have protective effects against diabetic nephropathy [94], and as the most potent natural ligand of FXR, CDCA can have important roles in the prevention of diabetic nephropathy [95]. However, since most probiotic bacteria are suppressed in the gut flora of diabetic patients [57], the loss of beneficial effects of these metabolites and neurotransmitters, probably contributes to the development of diabetes. Additionally, by intensifying the gut's mucosal inflammation, the reduction of probiotic species [33] can increase sympathetic activity [96], which can complicate the glycemic control in diabetic patients [97]. Taken together, through multiple mechanisms the gut microbiota can influence the development and progression of both type 1 and type 2 diabetes.

Lastly, diabetes can intensify the gut microbial dysbiosis and mucosal barrier dysfunction since hyperglycemia can alter composition of the gut flora by suppressing Lactobacilli [98]. This is compounded by subsequent development of eNOS deficiency [99] and the loss of interstitial cells of Cajal (ICCs) [100], resulting in stasis and bacterial overgrowth in the intestines of diabetic subjects [101]. Also, the development of diabetic microangiopathy can further compromise intestinal mucosal perfusion, thereby perturbing intestinal barrier function [52], and amplifying gut microbial dysbiosis [102] as observed in ischemia–reperfusion injury. The above information demonstrates the complex bidirectional relationship between the gut microbiota and the metabolic/endocrine system and their role in the pathogenesis of diabetes and diabetic nephropathy (Table 4).

Animal models

Up to know, we have discussed various pathogenetic mechanisms regarding microbiota, CKD, diabetes and hypertension. Recently animal studies have also confirmed these mechanisms were in fact true. Sun et al. showed that in a mouse model of obesity, high-fat diet (HFD) HFD-induced obesity leads to elevations in gut microbiota-generated metabolite TMAO in the circulation, which contributes to renal interstitial fibrosis and dysfunction by promoting renal oxidative stress and inflammation [103]. In another animal study, Wu et al. showed that fecal metabolites were significantly altered in rats with uremia; these changes were partially reversed by Lactobacillus [104].

Yoshifuji et al. demonstrated that rats treated with Lactobacillus showed decreased protein excretion attenuated systemic inflammation as evaluated by serum lipopolysaccharide, interleukin-6 and C-reactive protein levels in rats

Table 4 The relationship between gut microbiota and diabetes

- Fecal transplantation studies have shown that alterations of the gut microbiota directly affect the course of both type 1 and type 2 diabetes development [Refs. 54, 55]
- Gut mucosal barrier function is compromised in both type 1 and type 2 diabetes [Refs. 56, 57]
- In diabetic conditions Lactobacilli, Bifidobacteria, Pseudobutyrivibrio, Roseburia, and Faecalibacterium are reduced while *Clostridium perfringens*, Bacteroides spp., Prevotella, Betaproteobacteria, and Desulfovibrio are enriched [Refs. 5, 33]
- Immune system dysregulation due to gut dysbiosis may be observed during diabetes [Refs. 69, 72–75]
- Glucagon-like peptide—which has a protective role in gut mucosal barrier—secretion decreases in diabetes [Ref. 84]
- Diabetes can intensify the gut microbial dysbiosis and mucosal barrier dysfunction since hyperglycemia can alter composition of the gut flora by suppressing Lactobacilli [Ref. 98]
- Probiotic treatment such as with *Lactobacillus casei* CCFM419 had a positive effect on insulin resistance, increased the level of short-chain fatty acids and increased the abundance of butyrate-producing bacteria, such as Allobaculum and Bacteriodes [Ref. 107]
- Probiotic treatment such as with *Lactobacillus rhamnosus* NCDC 17 improved oral glucose tolerance test, biochemical parameters (fasting blood glucose, plasma insulin, glycosylated hemoglobin, free fatty acids, triglycerides, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol) and oxidative stress [Ref. 108]

by 5/6 nephrectomy (Nx rats). Histologically, renal sclerosis in Nx rats was restored by Lact treatment. A reduction in the expression of tight junction proteins and the Toll-like receptor 2 (TLR2), a putative Lact receptor, in the colons of Nx rats were mitigated by Lactobacillus [3]. Marques et al. evaluated the effect of a high-fiber diet and supplementation with the short-chain fatty acid acetate on the gut microbiota and the prevention of cardiovascular disease in sham and mineralocorticoid-excess-treated mice with a control diet, high-fiber diet, or acetate supplementation. They found that high consumption of fiber modified the gut microbiota populations and increased the abundance of acetate-producing bacteria independently of mineralocorticoid excess. Both fiber and acetate decreased gut dysbiosis, measured by the ratio of Firmicutes to Bacteroidetes, and increased the prevalence of *Bacteroides acidifaciens*. Compared with mineralocorticoid-excess mice fed a control diet, both high-fiber diet and acetate supplementation significantly reduced systolic and diastolic blood pressures, cardiac fibrosis, and left ventricular hypertrophy. Acetate had similar effects and markedly reduced renal fibrosis [105].

Whether altered GIS permeability by altered microbiata is an unknown issue, a recent study by Stewart et al. showed that hypertension changes the mechanical changes of rat gut. In their study, they evaluated the hypothesis that hypertension increases fibrosis and thus mechanical properties of the gut. A custom indentation system was used to test colon samples from Wistar Kyoto (WKY) normotensive rats and spontaneously hypertensive rats (SHR). They observed that SHR proximal colon has a mean steady-state modulus almost 3 times greater than WKY control rat colon (5.11 ± 1.58 and 18.17 ± 11.45 kPa, respectively). These increases were associated with increase in vascular smooth muscle cells layer and collagen deposition in the intestinal wall in the SHR [106].

Li et al. investigated the effect of *Lactobacillus casei* CCFM419 on insulin resistance and gut microbiota in type 2 diabetic mice. They showed that revealed that *L. casei* CCFM419 had a positive effect on insulin resistance. Furthermore, treatment with *L. casei* CCFM419 recovered the level of SCFA and increased the abundance of butyrate-producing bacteria, such as Allobaculum and Bacteriodes [107].

Singh et al. in a rat model also demonstrated that *Lactobacillus rhamnosus* NCDC 17 improved oral glucose tolerance test, biochemical parameters (fasting blood glucose, plasma insulin, glycosylated hemoglobin, free fatty acids, triglycerides, total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol), oxidative stress (thiobarbituric acid reactive substance and activities of catalase, superoxide dismutase, and glutathione peroxidase in blood and liver), bifidobacteria and lactobacilli in cecum, expression of glucagon-like peptide-1 producing genes in cecum, and adiponectin in epididymal fat, while decreased

propionate proportions (%) in caecum, and expression of tumor necrosis factor-α and interleukin-6 in epididymal fat of diabetic rats as compared to diabetes control group [108].

Human studies

In one open label controlled trial, 20 peritoneal dialysis (PD) patients habitually consuming a high AGE diet were recruited and randomized into either continuing the same diet (HAGE, $n = 10$) or a one-month dietary AGE restriction (LAGE, $n = 10$). At baseline, cohort exhibited a lower relative abundance of Bacteroides and Alistipes genus and a higher abundance of Prevotella genus when compared to the published data of healthy population. Dietary AGE restriction altered the bacterial gut microbiota with a significant reduction in *Prevotella copri* and Bifidobacterium animalis relative abundance and increased *Alistipes indistinctus, Clostridium citroniae, Clostridium hathewayi*, and *Ruminococcus gauvreauii* relative abundance [109].

Rossi et al. evaluated whether synbiotic (pre- and probiotic) therapy alters the gut microbiota and reduces serum concentrations of microbiome-generated uremic toxins, indoxyl sulfate (IS) and *p*-cresyl sulfate (PCS), in patients with CKD. Of 37 individuals randomized (age $= 69 \pm 10$ years old; 57% men; eGFR $= 24 \pm 8$ ml/min per 1.73 m^2), 31 completed the study. Synbiotic therapy did not significantly reduce serum IS but did significantly reduce serum PCS Synbiotics also altered the stool microbiome, particularly with enrichment of Bifidobacterium and depletion of Ruminococcaceae [110].

Fangmann et al. involved more than 500 human prediabetes and type 2 diabetes. Subjects with different metabolic phenotypes regarding their niacin [nicotinic acid (NA) and nicotinamide (NAM)] status and their gut microbiome. In addition, NA and NAM delayed-release microcapsules were engineered and examined in vitro and in vivo in two human intervention studies (bioavailability study and proof-of-concept/safety study). They showed that na and nam microcapsules produced a significant increase in the abundance of *Bacteroidetes*. In the absence of systemic side effects, these favorable microbiome changes induced by microencapsulated delayed-release NA were associated with an improvement of biomarkers for systemic insulin sensitivity and metabolic inflammation. Authors suggest that targeted microbiome intervention by delayed-release NA might represent a future therapeutic option for prediabetes and type 2 diabetes [111].

Soleimani et al. determined the effects of probiotic supplementation on glycemic control, lipid concentrations, biomarkers of inflammation and oxidative stress in 60 diabetic patients on hemodialysis in a parallel randomized double-blind placebo-controlled clinical trial Subsequently, they

were randomly divided into two groups to take either a capsule containing the probiotics Lactobacillus acidophilus, Lactobacillus casei and Bifidobacterium bifidum or placebo for 12 weeks. After the 12 weeks, analysis of patients who received probiotic supplements compared with the placebo showed they had significantly decreased fasting plasma glucose, serum insulin, homeostasis model of assessment-estimated insulin resistance, homeostasis model of assessment-estimated beta-cell function, Additionally, compared with the placebo, probiotic supplementation resulted in significant reductions in serum high-sensitivity C-reactive protein plasma malondialdehyde subjective global assessment scores, and a significant increase in plasma total antioxidant capacity [112].

Balfegó et al. in a pilot randomized trial investigated the effects of sardine-enriched diet on metabolic control, inflammation and gut microbiota in drug-naïve patients with type 2 diabetes: a pilot randomized trial. 35 drug-naïve patients with type 2 diabetes were randomized to follow either a type 2 diabetes standard diet (control group: CG), or a standard diet enriched with 100 g of sardines 5 days a week (sardine group: SG) for 6 months. There were no significant differences in glycemic control between groups at the end of the study. Both dietary interventions decreased phylum Firmicutes and increased *E. coli* concentrations at the end of the study from baseline, whereas SG decreased Firmicutes/Bacteroidetes ratio and increased Bacteroides–Prevotella compared to baseline [113].

Simon et al. performed a prospective, double-blind, randomized trial performed in 21 glucose-tolerant humans. Participants ingested 10(10) b.i.d. *L. reuteri* SD5865 or placebo over 4 weeks. In glucose-tolerant volunteers, daily administration of *L. reuteri* SD5865 increased glucose-stimulated GLP-1 and GLP-2 release by 76% ($P < 0.01$) and 43% ($P < 0.01$), respectively, compared with placebo, along with 49% higher insulin ($P < 0.05$) and 55% higher C-peptide secretion ($P < 0.05$) [114].

Modifying the gut microbiota to prevent/treat CKD and its risk factors

Given that in several ways the gut microbiota can influence the development of CKD and its major risk factors including inflammation, proteinuria, hypertension, and diabetes, it is reasonable to consider the gut microbiota as a target for prevention and treatment of these diseases. The strategies in the "engineering" of the gut microbiota can be grouped primarily into lifestyle changes and medications.

The lifestyle modification is an effective way to mold the gut microbiota into a healthier phenotype. To begin with, a fruit/vegetable-based diet enriched with prebiotics instead of a protein and animal fat-rich diet supports the growth of Prevotella, Lactobacilli, and Bifidobacteria [115, 116] while suppressing Bacteroides, Enterobacteria, and Clostridia [116, 117]. In fact consumption of a diet enriched with amylose, a fermentable and indigestible complex carbohydrate has been shown to markedly attenuate inflammation and oxidative stress, reduce renal fibrosis, retard progression of kidney disease, improve gut microbial dysbiosis and ameliorate metabolic disorders in CKD animals [118, 119]. In addition meeting the body's protein needs from plants seems healthier since a plant-based diet contains less choline and L-carnitine which are the precursors of the uremic toxin TMAO than animal-based diet [120]. In fact, dietary fibers and prebiotics have been shown to decrease inflammation and mortality in CKD patients [121] while retarding the decline in glomerular filtration rate [122], reducing insulin resistance [123], postprandial glycemia [124], blood lipid levels [125], and hypertension [126, 127]. Also, supplementing the diet with L-arginine, vitamin D, polyphenols, zinc, and iron strengthen the gut barrier [128] and enrich beneficial bacteria [129] while fish oil and plant-derived essential lipids suppress the pathogenic species [130]. Additionally, physical activity promotes a healthier gut flora by increasing the growth of beneficial bacteria and overall diversity of the gut microbiota [131] which can partly account for the overall health benefits of physical activity.

In addition to the diet and physical activity, use of various probiotics may re-shape the gut microbiota. First of all, probiotics such as Lactobacilli and Bifidobacteria can be effective in making the gut flora healthier by supporting the growth of other beneficial species including SCFA-producing bacteria [60]. In fact, although not all [132], several studies have reported the anti-inflammatory effects of probiotic and symbiotic bacteria in different patient populations [133]. Also, probiotics have been shown to lower blood urea nitrogen (BUN) level [134, 135] and improve the kidney function in diabetic patients [136], reduce arterial pressure [137], the risk of proteinuric kidney disease [138], and type 1 diabetes [70, 139], in the general population and mitigate the metabolic derangements in patients with type 2 diabetes [140]. Alternatives to the mainstream probiotic species are the archaea *Methanomassiliicoccus luminyensis* B10, which degrades TMAO [141], and the genetically engineered "smart bacteria", which have been shown to reduce BUN in uremic rats [142]. Other than live microorganisms, lubiprostone and the anti-diabetics liraglutide, saxagliptin, and metformin as well as some traditional medicines can promote the growth of beneficial genera including Lactobacilli, Eubacterium, Prevotella, and *Akkermansia muciniphila* [102] which is an anti-inflammatory species that has been shown to improve the metabolic profile in mice [143] while decreasing the level of Clostridium spp. [144]. and Firmicutes [145]. In general; the traditional medicines rhubarb (emodin) [144] and lubipristone [146] are able to reduce

Table 5 Treatment and prevention strategies of gut dysbiosis

Since gut microbiota can influence the development of CKD and its major risk factors including inflammation, proteinuria, hypertension, and diabetes, it is reasonable to consider the gut microbiota as a target for prevention and treatment of these diseases

The strategies in the "engineering" of the gut microbiota can be grouped primarily into lifestyle changes and medications

Lifestyle changes include
 - A fruit/vegetable-based diet enriched with prebiotics instead of a protein and animal fat-rich diet [Refs. 115, 116]
 - Consumption of a diet enriched with amylose [Refs. 118, 119]
 - Plant-based diet instead of animal-based diet [Ref. 120]
 - Increase dietary fiber [Refs. 121–127]
 - Supplementing the diet with L-arginine, vitamin D, polyphenols, zinc, and iron [Ref. 128]
 - Supplementing the diet with fish oil and plant-derived essential lipids [Ref. 130]
 - Increase exercise

Probiotic treatment
 - Probiotics such as Lactobacilli and Bifidobacteria can be effective in making the gut flora healthier by supporting the growth of other beneficial species including SCFA-producing bacteria [Ref. 60]
 - Probiotics have been shown to lower blood urea nitrogen (BUN) level [Refs. 134, 135]
 - Probiotics have been shown to improve the kidney function in diabetic patients [Ref. 136]
 - Probiotics have been shown reduce arterial pressure [Ref. 137],
 - Probiotics have been shown reduce the risk of proteinuric kidney disease [Ref. 138]
 - Probiotics have been shown reduce the risk of and type 1 diabetes [Refs. 70, 139], in the general population and
 - Probiotics have been shown mitigate the metabolic derangements in patients with type 2 diabetes [Ref. 140]

serum concentrations of uremic toxin. Moreover, besides the gut microbiota itself, their toxic by-products can be targeted via adsorption of uremic toxins and LPS. In fact AST-120 [147] and sevelamer [148] have been shown to reduce plasma levels of LPS and indoxyl sulfate respectively in hemodialysis [148] and CKD [147] patients. Also, there are strategies to inhibit production of indoxyl sulfate and TMAO by blocking the hepatic sulfation of indoxyl [149] and using the trimethylamine (TMA) inhibitor [150]. Therefore, the gut microbiota and its toxic products can be modified by certain dietary and therapeutic interventions (Table 5).

Conclusion

CKD development is a multifaceted process which involves an intricate bidirectional crosstalk between the intestines and the renal, metabolic, endocrine, and cardiovascular systems. The gut microbiota can exert protective or damaging impact on the kidney either directly or indirectly by modulating the major risk factors for development and progression of CKD including inflammation, diabetes, hypertension, and proteinuria. Given the important role of the gut microbiota in the development and progression of CKD and its main underlying causes, strategies aimed at improving the composition of the gut microbiota is an appealing approach for their prevention and treatment. Accordingly deciphering the cross talk between the gut microbiota and the renal, cardiovascular, endocrine, and metabolic systems is essential for developing novel strategies for prevention and treatment of chronic disorders such as CKD and its risk factors.

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