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REVIEW ARTICLE

Gut microbiota and inflammation in chronic kidney disease and their roles in the development of cardiovascular disease

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Abstract

The health and proper functioning of the cardiovascular and renal systems largely depend on crosstalk in the gut–kidney–heart/vessel triangle. Recent evidence suggests that the gut microbiota has an integral function in this crosstalk. Mounting evidence indicates that the development of chronic kidney and cardiovascular diseases follows chronic inflammatory processes that are affected by the gut microbiota via various immune, metabolic, endocrine, and neurologic pathways. Additionally, deterioration of the function of the cardiovascular and renal systems has been reported to disrupt the original gut microbiota composition, further contributing to the advancement of chronic cardiovascular and renal diseases. Considering the interaction between the gut microbiota and the renal and cardiovascular systems, we can infer that interventions for the gut microbiota through diet and possibly some medications can prevent/stop the vicious cycle between the gut microbiota and the cardiovascular/renal systems, leading to a decrease in chronic cardiovascular and renal diseases.

Keywords Gut microbiota · Chronic kidney disease · Uremic toxins · Cardiovascular disease

Introduction

The internal homeostasis of the human body largely depends on the interactions between bacteria and human cells, which have a normal composition ratio of 1.3:1 [1]. The gut microbiome is the best represented group [1], with widespread effects on the functioning and pathogenesis of each system of the body, including the renal [2] and cardiovascular [3] systems.

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The gut microbiota consists of 10^{14} bacteria [4] with tremendous diversity [5]. In healthy adults, Firmicutes and Bacteroidetes are the dominant phyla [5]. The gut microbiota contributes to the health of the host by protective and trophic functions [6] in addition to aiding host metabolism by synthesizing conjugated linoleic acid [7], amino acids such as lysine [8], vitamin B complex [9], and vitamin K [10] and by facilitating the absorption of complex carbohydrates [11]. Additionally, the gut microbiota communicates with the rest of the body primarily via its interactions with the immune system [12] and its metabolic products, such as uremic toxins [2], oxalate [13], bile acids [14], short-chain fatty acids (SCFAs) [15], nitric oxide (NO) [16], vitamin K [10], vitamin B complex [17], threonine [18], microRNAs (miRNAs) [19], gut hormones [20], neurotransmitters [21], the autonomic nervous system (ANS), and the enteric nervous system (ENS) [22] and through effects on intestinal expression of cannabinoid receptor CB1 [23].

Previous studies have demonstrated profound changes in the composition of the gut microbial community in patients and animals with chronic kidney disease (CKD) [24]. The diversity and ratio of bacterial species change in CKD and cardiovascular disease (CVD) patients, implicating possible bidirectional crosstalk between the gut microbiota and the renal and cardiovascular systems [25–27]. In fact,

spontaneously hypertensive rats (SHRs) were found to have decreased microbial richness with an increased Firmicutes/Bacteroidetes ratio [28], whereas end-stage renal disease (ESRD) patients were reported to have increased microbial diversity, with an increase in Firmicutes, Actinobacteria, and Proteobacteria and a decrease in Bifidobacteria and Lactobacilli [29]. A meta-analysis indicated that correction of the bacterial composition of the gut microbiota by prebiotics, probiotics, and synbiotics reduced the serum levels of uremic toxins, such as p-cresyl sulfate (p-CS) and indoxyl sulfate (IS) [30], which were found to have detrimental effects on renal and cardiovascular health [31]. Therefore, management of the gut flora through diet and medications can start a new trend in the treatment and prevention of CKD and CVD (Table 1).

The gut microbiota regulates inflammatory processes directly and indirectly

Modulation of the local and systemic inflammatory profiles is one of the mainstays of communication between the gut microbiota and the host. This "communication" takes place as direct and indirect interactions of the gut microbiota with the host, as detailed below.

The gut microbiota directly manipulates the host inflammatory response through its interactions with mucus [32] and epithelial barriers [33, 34] of the intestinal mucosa and immune cells [35]. Probiotic and commensal bacteria prevent development of local and systemic inflammation due to leakage of bacterial products, such as lipopolysaccharide (LPS), into the circulation via strengthening gut barrier function through various mechanisms [36, 37]. Increasing the secretion of antimicrobials, such as β-defensin, secretory IgA [36], and NO [16], enhancing mucus production, stabilizing the tight junctions between intestinal epithelial cells (IECs) [36], and suppressing the inflammatory response from IECs [34], are among the gut barrier-strengthening mechanisms. Furthermore, the gut microbiota can indirectly reduce intestinal permeability through selectively reducing intestinal expression of CB1, which is a cannabinoid receptor found to augment gut mucosal permeability [23]. Similarly, gut permeability can be deceased by species such as Lactobacillus and Bifidobacterium through glucagon-like peptide (GLP)-2 [37]. Finally, the commensal bacteria *Bacteroides fragilis* [38] and *Clostridia* (except for pathogenic strains) [39] have been found to increase regulatory T (Treg) cell activity and downregulate T helper 17 (Th17) cell immunity, thereby contributing to a more anti-inflammatory environment. Conversely, an environment devoid of chronic intestinal inflammation with proper gut barrier function cannot be preserved during gut dysbiosis [40] since dysbiosis involves a reduction of the majority of the commensal bacteria and an increase in certain phyla, such as Proteobacteria and Actinobacteria [28, 29], which are associated with a disturbance in the Th17/Treg balance in favor of Th17 in the intestines [35]. Moreover, Proteobacteria [29] together with TM7 bacteria are associated with a more permeable intestinal mucus barrier, which reduces the intestinal barrier performance [32].

As suggested, the gut microbiota can establish efficient crosstalk with the rest of the body through a number of mediators. Interestingly, the metabolic end products of the

Table 1 Effects of the purported mediators acting on the gut microbiota–inflammatory system interaction on the host inflammatory status

Pro-inflammatory	Anti-inflammatory	Variable effect[a]
p-cresyl sulfate [41, 42]	SCFAs [46]	miRNAs [56]
Indoxyl sulfate [43, 44]	NO [47][b]	Bile acids [50]
TMAO [45]	Vitamin K [51]	NE [63]
Oxalate [48, 49]	Vitamin B complex [17, 52–54]	ANS [66, 99]
Serotonin [62]	Threonine [55]	ENS [67]
	GLP-1 [57]	
	GLP-2 [58]	
	PYY [59]	
	GABA [60, 61]	
	ACh [65]	
	Dopamine [64]	
	H_2S [87, 88]	

[a]Some of these mediators have both pro- and anti-inflammatory effects

•miRNAs: miR455 is pro-inflammatory while miR10a and miR107 are anti-inflammatory [56]

•Bile acids: Most bile acids, especially lithocholic acid (LCA), are reported to have pro-inflammatory effects by themselves, while only ursodeoxycholic acid (UDCA) has been shown to suppress inflammation [50]. On the other hand, the activation of the bile acid receptors Farnesoid X Receptor (FXR) and TGR5 have an anti-inflammatory effect [50], chenodeoxycholic acid (CDCA) being the most potent activator of FXR [83]

•NE: Activation of the α-adrenergic receptors elicits pro-inflammatory effects while β-adrenergic receptor activity is anti-inflammatory [63]

•ANS: The parasympathetic nervous system (PNS) suppresses inflammation via activation of the ACh receptor α7nAChR [66]. On the other hand, the sympathetic nervous system (SNS) can exert both pro-inflammatory (via α_2-adrenergic receptors) and anti-inflammatory (via β_2-adrenergic receptors) effects [66], pro-inflammatory properties being more dominant [99]

•ENS: The inflammatory effects of ENS depends on the location of the intestinal macrophages they induce; the lamina propria macrophages (LpMs) are inclined to be pro-inflammatory while the muscularis macrophages tend to have an anti-inflammatory phenotype, having the anti-inflammatory β2-adrenoceptors [67]

[b]Even though NO can have pro-inflammatory activity via NF-κB activation, the number of mechanisms leading to its anti-inflammatory effects are more [47]

Table 2 The phyla of the gut bacteria involved in the regulation of the host inflammatory response

Firmicutes	Bacteroidetes	Proteobacteria	Actinobacteria	Verrucomicrobiaceae	Fusobacteria
Clostridium	*Bacteroides*	*Enterobacter*	*Bifidobacteria*		*Fusobacterium*
Lactobacillus	*Prevotella*	*Citrobacter*	*Propionibacterium*		
Streptococcus		*Escherichia*	*Eggerthella*		
Enterococcus		*Proteus*	*Collinsella*		
Eubacterium		*Edwardsiella*			
Butyrivibrio		*Acinetobacter*			
Megasphaera		*Oxalobacter*			
Roseburia		*Hafnia*			
Staphylococcus		*Klebsiella*			
Bacillus		*Morganella*			
Lactococcus		*Serratia*			
Leuconostoc		*Pseudomonas*			
Pediococcus		*Salmonella*			
Listeria		*Deltaproteobacteria*			
Peptostreptococcus		*Bilophila*			
Ruminococcus					
Peptococcus					
Lachnospiraceae					
Erysipelotrichaceae					

gut microbiota, including p-CS [41, 42]; IS [43, 44]; trimethylamine-*N*-oxide (TMAO) [45]; ammonia [24]; SCFAs [46]; NO [47]; oxalate [48, 49] and bile acids [50]; vitamin K [51]; vitamin B complex [17, 52–54]; threonine [55]; miRNAs [56]; gut hormones such as GLP-1, GLP-2, and peptide YY (PYY) [57–59]; neurotransmitters such as γ-aminobutyric acid (GABA), serotonin, norepinephrine (NE), dopamine (DA), and acetylcholine (Ach) [60–65]; the ANS [66]; and the ENS [67] have all been reported to influence the host inflammatory status. Taken together, these findings suggest that the gut microbiota is able to manipulate the inflammatory status of the host indirectly through an array of mechanisms (Tables 1 and 2).

The gut microbiota has different elements that control the production of metabolic and endocrine mediators and the activity of neurologic mediators, which are able to manipulate host inflammatory activity.

- In the case of metabolic mediators, species mostly belonging to Proteobacteria and some bacteria from the Firmicutes family produce pro-inflammatory uremic toxins [41–45, 68–71], whereas anti-inflammatory mediators, such as SCFAs and NO [46, 47], are produced by Lactobacilli and some other beneficial species belonging to the Firmicutes family, some species from the Bacteroides family, such as Bacteroides fragilis and Prevotellaceae, and Bifidobacteria [16, 71–75].
- The species producing SCFAs are also beneficial in terms of endocrine mediators, because SCFAs stimulate enteroendocrine cells to produce anti-inflammatory gut hormones, such as GLP-1, GLP-2, and PYY [57–59, 76–79].
- Likewise, other anti-inflammatory metabolic elements, including vitamin K and the group B vitamins [17, 51–54], are produced by these beneficial bacteria, although some species from the Proteobacteria family can contribute to their production [80–82].
- The beneficial bacteria, such as Lactobacilli and Bifidobacteria, are among the species producing chenodeoxycholic acid (CDCA), which is the most potent ligand of the anti-inflammatory Farnesoid X receptor [50, 83, 84] and has anti-inflammatory effects on renal tissue [85], and ursodeoxycholic acid (UDCA), which is an important anti-inflammatory bile acid [50] produced by Bifidobacteria [84]. In contrast, the pro-inflammatory bile acids DCA and lithocholic acid (LCA) [50] are mainly by-products of bile acid metabolism by species from genus Clostridium [84].
- Sulfur-reducing species from Proteobacteria produce H_2S [86], which is a strong anti-inflammatory gaseous signaling molecule [87] with renoprotective [88] and cardioprotective effects [89].
- Different neurotransmitters are produced by different bacteria; some Lactobacillus and Bifidobacteria species produce the anti-inflammatory neurotransmitters GABA and Ach, whereas some species from the Proteobacteria and Firmicutes families produce the pro-inflammatory neurotransmitter serotonin [60, 61, 65].

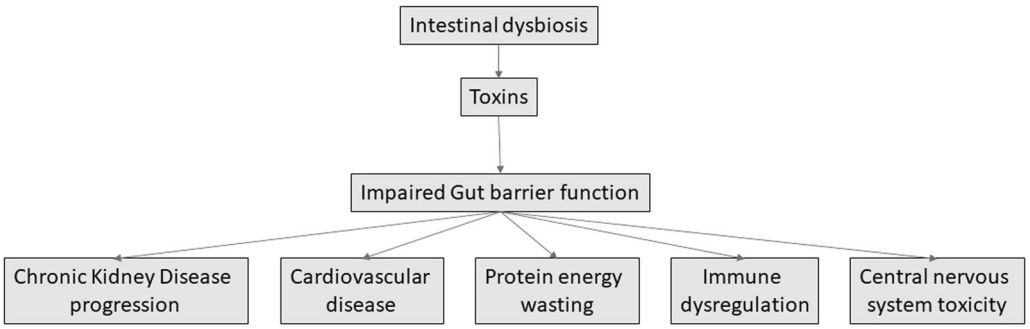

Fig. 1 Impact of dysbiosis on chronic kidney disease

- ANS activity can be modulated by the gut microbiota. A strain of Lactobacillus has been found to have inhibitory effects on renal sympathetic activity [90], and species from Lactobacilli and Bifidobacteria can indirectly reduce sympathetic activity through their analgesic and anxiolytic effects [91–96]. Furthermore, lactobacilli can induce the vagus nerve, which is known to have important anti-inflammatory effects [93, 97]. Conversely, SCFAs have stimulatory effects on the SNS [98], implying that all SCFA-producing bacteria can have a positive effect on SNS activity, which is inclined to be more pro-inflammatory [99]. However, since some Lactobacilli themselves reduce sympathetic activity [90] and induce vagal activity [93, 97] and SCFAs have overall anti-inflammatory effects [46], the production of a pro-inflammatory effect elicited by SCFA-producing bacteria through SNS activity is unlikely.
- Lastly, ENS activity is modulated by the gut microbiota; sulfur-reducing species from the Proteobacteria family increase ENS activity [86, 100], whereas *Bifidobacterium longum* has the opposite effect on the ENS [92]. Given that the lamina propria macrophages (LpMs) induced by the ENS tend to have pro-inflammatory effects [67], increased ENS activity by sulfur-reducing Proteobacteria itself may induce mucosal inflammation via LpM activity.

All in all, different groups of bacteria can be inferred to affect host inflammatory activity in different ways. For instance, the Bacteroides family, Bifidobacteria, Lactobacilli, and other species from the Firmicutes family mostly reduce inflammation, whereas species from Proteobacteria tend to be pro-inflammatory via metabolic, endocrine, and neurologic pathways (Table 2 and Fig. 1).

Gut–kidney crosstalk and inflammation in the development of CKD

Gut–kidney crosstalk, which is largely affected by the gut microbiota, plays an integral role in the development of CKD with reciprocal interactions [25]. The gut microbiota manipulates the processes leading to CKD through inflammatory [25], endocrine [20], and neurologic pathways [90]; a healthy gut microbiota protects the CKD, whereas gut dysbiosis contributes to the development of CKD [2]. In fact, CKD is associated with alterations in the gut microbiota; species producing uremic toxins, such as Enterobacteriaceae, Clostridiaceae, Pseudomonadaceae, and Bacteroidiaceae, are increased, whereas beneficial species, such as Lactobacillaceae, Bifidobacteriaceae, and Prevotellaceae, are decreased [101–104]. Consistently, fecal transplantation from CKD patients to antibiotic-treated mice results in an increase in the plasma TMAO levels [29]. In contrast, deterioration of kidney function disrupts the intestinal mucosal barrier and contributes to gut dysbiosis [25]. Therefore, CKD may plausibly result in a faulty bidirectional interaction between the gut microbiota and the kidneys.

As evidenced by many studies, including the Chronic Renal Insufficiency Cohort (CRIC) study, CKD is an outcome of chronic systemic inflammation [105, 106], which renders inflammation as one of the main crosstalk pathways between the gut microbiota and the kidney involved in the development in CKD. Given that gut dysbiosis accompanies CKD, we can speculate that gut dysbiosis supports a more pro-inflammatory environment in the host that eventually contributes to CKD progression. Generally, the species found to be increased in the gut flora of CKD patients tend to increase the host inflammatory response via a number of mechanisms. For example, these species generate the established pro-inflammatory substances uremic toxins [41–45, 68–71], DCA, and LCA [50, 84] and degrade the anti-inflammatory renoprotective neurotransmitter Ach [65, 107, 108]. Moreover, Proteobacteria, which is the phylum containing Pseudomonadaceae, have been found to deteriorate gut mucosal barrier function by increasing gut mucus permeability [32] and the intestinal Th17/Treg ratio [35]. Conversely, the species found to be decreased in CKD are among those that strengthen gut barrier function [16, 36, 37]; produce anti-inflammatory

SCFAs [46, 71, 73, 109], NO [16, 47], CDCA, UDCA [50, 83–85], GABA [60, 61, 110], Ach [65, 107, 108], and the vitamin B complex [17, 52–54, 81, 82]; increase the production of gut hormones with anti-inflammatory properties [57–59, 76–79]; increase anti-inflammatory vagal activity [90, 93, 97]; and decrease pro-inflammatory renal sympathetic activity. Interestingly, CKD is associated with gut barrier dysfunction, an increase in uremic toxins [101], elevated renal sympathetic activity [111], lower group B vitamin levels [112–114] and NO [115], and a reduction in vagal activity [116], which may stem from the gut dysbiosis found in patients with CKD. Therefore, we can suggest that a healthy gut microbiota can protect from CKD, whereas gut dysbiosis takes part in the development and progression of CKD through a number of pathways that manipulate host inflammatory activity.

Another pathway through which the gut microbiota can affect kidney function is the metabolic/endocrine interaction of the gut with the kidney. The gut microbiota acts like an endocrine organ by producing several neurotransmitters and affects intestinal endocrine activity. Species from Lactobacillaceae, Prevotellaceae, and Bifidobacteriaceae synthesize the neurotransmitters GABA and Ach [107, 110] and promote intestinal production of the incretins GLP-1, GLP-2, and PYY [76–79]. These neurotransmitters and hormones modulate renal function; for example, GABA can induce natriuresis [117] and suppress renal sympathetic nerve activity [117], Ach increases the glomerular filtration rate (GFR) by promoting renal vasodilatation [118], and GLP-1 increases the GFR, diuresis, and natriuresis while reducing proximal tubular sodium reabsorption and the angiotensin II (ANG II) level [119, 120]. PYY has controversial effects on renal function; it can reduce renal blood flow or increase diuresis/natriuresis and suppress plasma renin activity depending on the type of renal YY receptor it induces [121]. Additionally, by acting like hormones, the metabolic end products of these species, such as SCFAs and NO [16, 71, 73], can alter renal function. Activation of the renal SCFA receptor Olfr78 increases blood pressure in the physiological range by renin secretion, but this effect is counterbalanced or may even be reversed by the vasodilatory effect of the induction of the other SCFA receptors Gpr41 and Gpr43 [122–124]. Additionally, NO prevents ANG II and NE-dependent renal vasoconstriction [125]. In contrast, serotonin, which is produced by species from both Lactobacillaceae [126] and Bacteroidiaceae [127], induces renin release [128] and renal vasoconstriction via several different mechanisms [129–131]. Considering the "endocrine" activities of the gut microbiota on the kidneys, clearly the species that are reduced in the gut microbiota of CKD patients can actually provide renoprotection through reducing renin– angiotensin–aldosterone system activity [132] and favoring lower blood pressure [133] by reducing renin–angiotensin–aldosterone and renal sympathetic activity while increasing renal perfusion, diuresis, and natriuresis. Thus gut dysbiosis can be considered a reason for CKD progression via disruption of endocrine gut–kidney interactions.

Furthermore, the gut microbiota can interact with the kidneys via the ANS. A number of bacteria can modulate the functioning of the ANS. For example, some species from Lactobacillaceae can induce vagal activity [90, 93] and reduce renal sympathetic activity [90]. In addition to their analgesic and anxiolytic effects, some Lactobacilli and Bifidobacteria [91–96] can indirectly decrease the sympathetic tone of the host since both pain [134, 135] and anxiety [136] elevate sympathetic activity. Conversely, SCFAs have been found to have sympathoexcitatory effects [98], implying that all species that produce SCFAs, including Lactobacillaceae, Bifidobacteriaceae, and Prevotellaceae, have the potential to increase sympathetic activity. However, given that SCFAs can reduce blood pressure at the level of receptors [123], the possibility of a rise in sympathoexcitation-related blood pressure due to SCFA-producing bacteria is unlikely. The inflammatory conditions in the intestines can alter colonic sympathetic activity; for instance, ulcerative colitis increases sympathetic induction, whereas Crohn's disease causes a decrease in sympathetic activity by damaging the sympathetic fibers [137]. Taking into account that inflammation in ulcerative colitis remains superficial and the reduced sympathetic activity in Crohn's disease is probably due to injury to the sympathetic nerves, we can deduce that mucosal inflammation can cause sympathoexcitation. Furthermore, considering that Proteobacteriaceae can predispose the gut mucosa to inflammation [32, 35], these species may cause sympathoexcitation. Therefore, all things considered, gut dysbiosis in CKD patients may disturb the balance of ANS function in favor of SNS activity, which is an important contributor to progression of CKD [138].

Lastly, deterioration of renal function deepens derangement in the gut microbiota and mucosal integrity. Some purported metabolic mechanisms for this condition are expansion of uremic toxin-producing species with contraction of carbohydrate-fermenting SCFA-producing species for increased uremic toxin conservation and damage to the gut mucosa due to retention of uremic toxins, metabolic acidosis, fluid retention, and resulting intestinal congestion [25]. In addition, the increase in the urea level and its diffusion into the intestinal tract play important roles in alteration of the microbiome by mediating expansion of urease-possessing bacterial species [24]. Hydrolysis of urea in the gut lumen by these bacteria results in formation of ammonia and ammonium hydroxide, which disrupt the

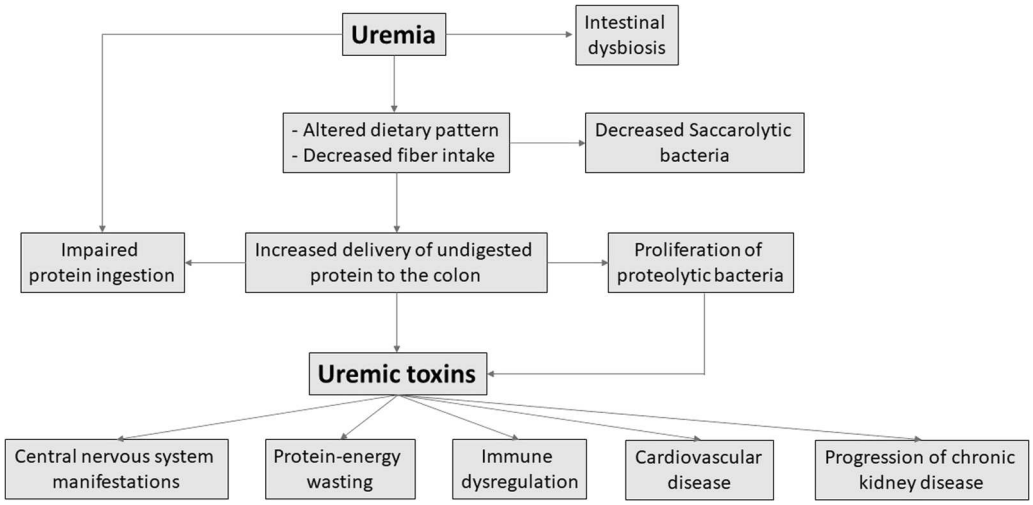

Fig. 2 Role of chronic kidney disease in the intestinal microbiota and its systemic effects

epithelial barrier by dissociating the sulfhydryl bonds in the tight junction and facilitate the entry of endotoxin and other noxious luminal contents into the intestinal wall, thereby causing local and systemic inflammation [139]. Moreover, the hormonal activity of the kidneys is changed in CKD patients, including an increase in the RAS activity [140] and reductions in the angiotensin-converting enzyme 2 [141], erythropoietin [142], and active vitamin D levels [143]. Importantly, these hormones have an effect on the gut microbiota and gut barrier function. ANG II can both damage the gut barrier [144] and cause dysbiosis with the reduction in butyrate-producing bacteria and the Bacteroidetes population due to hypertension [145], whereas angiotensin-converting enzyme 2 protects against intestinal inflammation [146]. Additionally, erythropoietin protects intestinal barrier function [147], and vitamin D provides a more immune-tolerant environment in the gut mucosa [148], further protecting the intestinal mucosal barrier from inflammatory destruction. Considering the alterations in renal hormone levels and the effects of these hormones on gut barrier function and the microbiota, CKD apparently worsens gut dysbiosis and mucosal damage not only at the metabolic level but also at the endocrine level (Fig. 2).

Gut–heart crosstalk and inflammation in the development of CVD

One important consequence of deranged crosstalk between the cardiovascular system and other organs is CVD. As an important modulator of gut–cardiovascular crosstalk, the gut microbiota is engaged in a bidirectional relationship with the cardiovascular system [149, 150]. Compared to that of healthy cases, the gut microbiota of patients with atherosclerosis has more species from genus Collinsella and fewer from genera Bacterioides, Roseburia, and Eubacterium [151]. Additionally, the abundance of Lachnospiraceae and Erysipelotrichaceae in the gut flora is positively correlated with the total cholesterol and low-density lipoprotein (LDL)-cholesterol levels, and species from Proteobacteria colonize atherosclerotic plaques [152]. Gut dysbiosis is also evident in cases of hypertension and heart failure. In hypertension, an increased Firmicutes/Bacteroidetes ratio reduced SCFA-producing bacteria, such as Bifidobacterium, Bacterioidetes, and Roseburia, and increased Prevotella, Klebsiella (from Proteobacteriaceae) and the lactate-producing Streptococcus and Turicibacter (from Erysipelotrichaceae) are found in the gut microbiota [28, 153]. In patients with heart failure, species from genera Eubacterium and Dorea (from Clostridiaceae) are significantly reduced compared to that of the microbiota of the healthy controls [154]. Changes in the gut microbiota can affect cardiovascular health; in fact, transplantation of cecal contents from stroke-prone SHRs to normotensive rats resulted in blood pressure elevation of the normotensive rats [155]. The gut microbiota can affect cardiovascular function principally through inflammatory, metabolic/endocrine, and neurologic pathways [156]. In turn, deterioration of cardiovascular function worsens gut barrier dysfunction and dysbiosis [150], creating a vicious cycle resulting in aggravation of CVD.

CVD is closely associated with chronic systemic inflammation [157], and the gut microbiota can affect the course of CVD development through its effects on inflammatory processes [158]. The gut microbiota can alter the host's tendency for inflammation through direct effects on gut barrier function [29]; interactions with Th cells [39]; and metabolic, endocrine, and neurologic activities [156]. In fact, gut barrier dysfunction can promote CVD development [159]. Bacteria supporting a more immunotolerant environment, such as Bacterioides [38] and Clostridia [39],

are decreased in patients with hypertension and heart failure [153, 154]. Additionally, lactate, which is a pro-inflammatory metabolite [160] associated with hypertension [161], is produced by species such as Streptococcus and Turicibacter, which are enriched in the gut flora in hypertension cases [28]. These issues are highly important because hypertension is an autoimmune and inflammatory disease [162].

Other pro-inflammatory metabolites contributing to the development of CVD include the uremic toxins [41–45, 163, 164], which are produced by species such as Lachnospiraceae, Prevotella [165], Proteobacteria [68, 70], and Erysipelotrichaceae [166]. Interestingly, these bacteria are also increased in the gut microbiota of patients with atherosclerosis and hypertension [152, 153]. However, CVD is associated with loss of some beneficial bacteria, such as Bacterioides, Bifidobacterium, Roseburia, and Eubacterium [28, 151, 153, 154], which are known to primarily produce SCFAs [72–74], vitamin K [80], vitamin B complex [81], and GABA [110], which are mediators with anti-inflammatory properties [17, 46, 51–54, 60, 61]. Since SCFAs also promote the production of anti-inflammatory gut hormones [57–59, 76–78], a decrease in SCFA-producing bacteria leads to a loss of "the endocrine protection method" from inflammation. Overall, by increasing the tendency of the host toward inflammation, gut dysbiosis can promote sympathetic activity since pro-inflammatory cytokines can induce SNS centrally [167]. In turn, SNS activity increases the blood pressure and has mostly pro-inflammatory properties [99], which can worsen CVD in general [157].

The metabolic end products and the effects of the gut microbiota on gut endocrine activity can influence the process of CVD development. Acting like an endocrine organ, the gut microbiota produces several neurotransmitters and metabolites that affect cardiovascular health. For example, Bifidobacteria, which are reduced in hypertension cases [153], produce GABA, which centrally prevents hypertension via its control over the SNS [168]. The loss of SCFA-producing bacteria in the gut microbiota can cause CVD by abolishing the antiatherogenic [169] and antihypertensive effects of the SCFAs [123]. On the other hand, species from Proteobacteria produce serotonin, NE, and DA [170], which are neurotransmitters with pro-hypertensive and pro-atherogenic properties [171–173], with the exception of DA [174–176]. Furthermore, the gut microbiota controls the endocrine activities of the intestine; for example, SCFA-producing bacteria, which are reduced in CVD cases [28, 151, 153, 154], promote secretion of incretins with cardioprotective, antiatherogenic, and antihypertensive properties [177–180], except for PYY [181, 182]. Therefore, the gut dysbiosis seen in CVD cases gives rise to an endocrine environment favoring CVD development.

Another pathway through which the gut microbiota affects cardiovascular health is modulation of the SNS. For example, Bifidobacteria can suppress SNS activity via the central effects of GABA, thereby protecting from hypertension [168]. Consistently, the gut microbiota contains less-than-normal Bifidobacteria in hypertension patients [153]. Moreover, gut mucosal inflammation deteriorates the mucosal barrier function, which can result in translocation of bacteria and bacterial products into the bloodstream and induction of pro-inflammatory cytokine secretion [159]. Since pro-inflammatory cytokines can stimulate the SNS centrally [167], we can hypothesize that any type of gut dysbiosis that compromises gut barrier function can increase the sympathetic tone of the host. Considering that sympathetic hyperactivity causes hypertension and other CVDs [183], the reason underlying CVD development in people with gut dysbiosis seen in cases of CVD may be partially due to sustained SNS activation by the dysbiotic gut microbiota.

The role of advanced glycation end products (AGEs) in CKD and CVD and their relationships with the gut microbiota also warrant mention. AGEs are a heterogeneous group of molecules, such as sugars, lipids, and nucleic acids, which are formed by nonenzymatic glycation reactions through a complex sequence of reactions referred to as Maillard reactions [184]. AGEs bind to cell surface receptors, such as AGER1 or, most importantly, to the receptor for AGEs (RAGE) [185].

The RAGE–AGE pathway is related to inflammation, oxidative stress, and endothelial dysfunction, which are all related to CKD and CVD [184, 186]. Vlassara et al. established for the first time that chronic intravenous injection of AGEs in healthy rats induced characteristic histological changes (glomerulosclerosis, mesangial matrix expansion, and basement membrane thickening) and albuminuria [187].

In addition, circulating AGE levels are independently associated with new or worsening nephropathy in type 2 diabetes (T2D) patients [188]. A direct role of AGEs in the development of cardiac dysfunction has been shown in animals [189]. However, some indirect arguments suggest a link. Abundant microvascular AGE deposition has also been observed in patients with diabetic cardiomyopathy [190] as well as within cardiomyocytes in epicardial biopsies from the hearts of patients undergoing transplantation [191]. This evidence strongly supports a role of AGEs as a risk factor for CKD and CVD.

In addition, recent evidence suggests that the gut microbiota and AGEs have a reciprocal relationship. Kinetic studies have estimated that 10–30% of consumed dietary AGEs (dAGEs) are absorbed in the upper intestine and enter the circulation [192]. The remaining AGEs escape digestion and reach the large bowel, where they undergo

anaerobic fermentation and may mutually modulate gut microbiota growth [193].

In vitro studies have indicated that Maillard reaction products may affect bacterial growth [194] and the gut microbiota composition and that micro-organisms can degrade dAGEs [194]. AGEs may affect the gut microbiota through negative selection (direct toxic effects) or positive selection (favoring overgrowth of bacterial species that can utilize AGEs as an energy source) [195]. In a recent trial, Yacoup et al. evaluated the effect of restricting habitually high dietary AGE consumption on the gut microbiota in a group of ESRD patients on maintenance peritoneal dialysis (PD) and hypothesized that dAGE restriction affected the diversity of the bacterial gut microbiota in patients with ESRD receiving maintenance PD. These authors showed that dietary intervention resulted in an increase in the Firmicutes abundance and a decrease in Verrucomicrobia [195].

Another study demonstrated the protective effects of rosmarinic acid (RA) and carnosic acid (CA) against streptozotocin-induced oxidation, glycation, inflammation, and microbiota imbalance in diabetic rats with prebiotic effects. Compared with those of the model rats, CA administration increased the ratios of Actinobacteria, Bacteroidetes, Proteobacteria, and Verrucomicrobia, whereas RA administration increased the ratios of Actinobacteria, Proteobacteria, and Verrucomicrobia. Interestingly, Fusobacteria was only detected in the feces of the diabetic rats administered RA and CA [196].

Another study showed that mice fed a typical Western diet (WD) demonstrated gut dysbiosis, mainly including reductions in Bifidobacterium species, increased arterial stiffness, endothelial dysfunction, and increases in circulating LPS-binding protein (LBP), interleukin (IL)-6, and phosphorylated nuclear factor-κB. Antibiotic treatment successfully abrogated the gut microbiota and reversed the WD-induced arterial stiffness and endothelial dysfunction. These improvements were accompanied by significant reductions in the LBP, IL-6, nuclear factor-κB, and AGEs [197].

Mastrocola et al. showed that a fructose diet, especially in solid form, resulted in gut dysbiosis, with increased colonization by Bacteroides, Lactobacillus, Lachnospiraceae, and Dorea and the accumulation of the AGEs *N* (epsilon)-(carboxymethyl)lysine and *N*(epsilon)-(carboxyethyl)lysine in the intestinal mucosa as revealed by immunofluorescence [198]. Qu et al. demonstrated that Sprague–Dawley rats exposed to a high-AGE diet showed richness of the microbiota, especially saccharolytic bacteria, such as Ruminococcaceae and Alloprevotella, although some putatively harmful bacteria (Desulfovibrio and Bacteroides) were also increased [199].

Finally, deteriorations in cardiovascular function further aggravate gut barrier dysfunction and dysbiosis [150]. As observed in congestive heart failure patients, gut mucosal permeability is increased and bacteria are more adherent to the gut mucosa, probably due to mucosal ischemia/hypoxia/edema [150]. Additionally, congestive heart failure leads to an increase in sympathetic activity, which can impair gut barrier function by causing mucosal ischemia due to reduced splanchnic blood flow [150] and via its pro-inflammatory effects on the gut mucosa [99]. In summary, development of cardiovascular impairment contributes to a vicious cycle, leading to progression of CVD by exacerbating gut dysbiosis and barrier dysfunction.

Cardiovascular–renal crosstalk, cardiorenal syndromes, and the gut microbiota

The cardiovascular system and the kidneys are intimately related to each other. Thus impairment in the functioning of either system deteriorates the functioning of the other, giving rise to cardiorenal syndromes [200, 201]. Basically, CKD can distort cardiovascular functions through uremic toxin retention, abnormalities in renal calcium/phosphate handling, overactivation of the SNS and RAS, anemia, and increased oxidative stress, resulting in the development of chronic renocardiac syndrome [200] and fluid overload. Moreover, chronic heart failure can compromise renal function via chronic renal hypoperfusion/congestion and consequent RAS activity, SNS activation, systemic inflammation, and RAS activation, giving rise to cardiorenal syndrome. In addition to this "ping–pong relationship" between the cardiovascular and renal systems, the gut microbiota can affect the development of chronic renocardiac syndrome. For example, the uremic toxins produced by the gut microbiota can aggravate chronic renocardiac syndrome via deleterious effects on both cardiovascular and renal health mostly through inflammatory pathways [202]. In fact, although the alterations detected in the gut microbiota of patients with CKD and CVD were not exactly the same, generally an increase in the uremic toxin-producing species, a decrease in SCFA-producing bacteria and compromise of the gut barrier function were evident [28, 101–104, 152, 159, 203].

To be more succinct, we will discuss some specific mechanisms and mediators of gut–cardiovascular and kidney crosstalk. Renal dysfunction causes not only metabolic derangements but also systemic inflammation, as indicated by elevation of C-reactive protein, pentraxin-3, pro-inflammatory cytokine sTWEAK (tumor necrosis factor-like weak inducer of apoptosis), sTRAIL (tumor necrosis factor-related apoptosis-inducing ligand), S100A12 (extracellular newly identified RAGE-binding protein), mannose-binding lectin, and activated complement levels [203, 204]. LPS-induced monocyte/macrophage activation and systemic inflammation can explain the persistent systemic inflammation in CKD/ESRD [203]. Moreover, the intestinal

microbiota is increasingly recognized as a modifier of the host immune system, especially polarization of T cell subsets and natural killer T cells [205, 206]. Edematous heart failure patients were shown to have high serum endotoxin and cytokine levels that declined upon diuretic therapy [207]. Wang et al. showed that experimental uremia in rats increased bacterial translocation from the gut into the mesenteric lymph nodes, liver, and spleen, which was associated with higher serum IL-6 and C-reactive protein levels [208]. Thus CKD-related dysbiosis and changes in the intestinal barrier may favor increased translocation of living bacteria or bacterial products from the intestinal lumen into the circulation, which is a process that can account for the persistent systemic inflammation in CKD patients and is also associated with CVD.

Increases in LPS may also be related to atherosclerosis via other mechanisms. For example, the LPS receptor Toll-like receptor 4 (TLR4) is a mediator of atherosclerosis, which may imply that increased LPS/TLR4 signaling can be a driving factor of accelerated atherogenesis in CKD/ESRD patients [209]. In addition, neutralizing the bacteria-derived uremic toxin IS inside the gut delays CKD and CVD progression in uremic rats [210].

Another mediator of gut–kidney and cardiovascular crosstalk may be TMAO, which is a gut microbiota-generated metabolite that is thought to play a role in endothelial dysfunction, inflammation, and CVD. Circulating TMAO is elevated in CKD. In a 5/6 nephrectomy model, Li et al. showed that the TMAO levels were markedly elevated in CKD-vehicle rats compared with those of sham-vehicle rats. However, rats treated with 1.0% 3,3-dimethyl-1-butanol (DMB, an inhibitor of trimethylamine (TMA) formation) for 8 weeks had reduced TMAO levels. Acetylcholine-induced endothelium-dependent vasodilation was impaired in CKD-vehicle rats compared with that of sham-vehicle rats, as indicated by the reduced maximal relaxation (Emax) and decreased area under the curve (AUC). The Emax and AUC were both normalized in the CKD-DMB rats. Molecular studies revealed that endothelial NO synthase (eNOS) activity was decreased and superoxide production and pro-inflammatory cytokine expression were increased in the aortas of CKD-vehicle rats compared with those of the sham-vehicle rats. Notably, the abnormalities in the above molecular parameters were completely restored in the CKD-DMB rats. These results suggest that CKD elevates circulating TMAO levels, which may reduce eNOS-derived NO production by increasing vascular oxidative stress and inflammation, thereby contributing to CKD-associated endothelial dysfunction and CVD [211].

Some other mediators and toxins may operate in this crosstalk. Among these toxins are IS, p-CS, and indole-3-acetic acid (IAA), which originate from bacterial protein fermentation in the large intestine. These toxins derived from tryptophan are ligands of the aryl hydrocarbon receptor, whose activation is involved in atherogenesis, vascular inflammation, and oxidative stress [212]. Recent studies have reported that these toxins induce pro-inflammatory responses and are reliable markers of CVD and mortality in CKD patients [213]. Borges et al. studied protein-bound uremic toxins from the gut microbiota and inflammatory markers in CKD. The total levels of uremic toxins (IS, p-CS, and IAA) were assessed by high-performance liquid chromatography with fluorescence detection. The C-reactive protein, IL-6, monocyte chemoattractant protein-1 (MCP-1), and calprotectin plasma levels were determined by immunometric assays. Hemodialysis (HD) patients presented higher inflammatory markers and uremic toxin levels than the nondialysis patients. The IL-6 levels were positively correlated with IS, p-CS, and IAA. A positive correlation was also observed for the MCP-1 levels with IS, p-CS ($r = 0.48$; $P < 0.001$), and IAA [212].

Therefore, we can sensibly consider CKD and CVD as the two interlinked causes and consequences of gut barrier dysfunction and dysbiosis that form an ominous gut–kidney–heart/vessel triangle, resulting in cardiorenal syndromes with gut dysbiosis and compromised gut barrier dysfunction.

Gut microbiota as a new target for the prevention and treatment of CKD and CVD

Current understanding of the role of the gut microbiota in cardiovascular and renal health has led to the development of new strategies to protect the balance of the gut microbiota and prevent dysbiosis. Indeed, metabolic phenotyping of biological systems has proven its application in characterizing metabolites and providing novel insights into gene–environmental–gut microbiome interactions in relation to a disease state [214]. These efforts can be grouped into four categories: probiotic use, diet modification, medications, and exercise.

The gut microbiota can be reconstructed with the use of beneficial bacteria. Probiotics are live bacteria with moderating properties on inflammation [215], such as Lactobacilli, Bifidobacteria, and Streptococci [216]. In fact, treatment with Lactobacillus species resulted in a reduction of the atherosclerotic burden in ApoE 2/2 mice [217] and decreased the serum levels of endotoxins and pro-inflammatory cytokines while increasing those of anti-inflammatory cytokines, thereby preserving residual renal function in PD patients [218]. Additionally, *Methanomassiliicoccus luminyensis* B10, which is a strain of archaea, has been shown to degrade TMAO and has been suggested for utilization as a probiotic [219]. Therefore, engineering the gut microbiota via beneficial

microorganisms can be a modality to prevent or even treat CVD and CKD.

Our diet feeds not only us but also the bacteria in our gut flora. For example, protein and animal fat-rich diets favor the growth of Bacteroides species, whereas carbohydrate-rich diets expand Prevotella species in the gut microbiome [220]. Therefore, modifications of dietary habits can support a healthier gut microbiota. For example, a fruit/vegetable-rich diet with flavonoid intake suppresses growth of pathogenic Clostridia [221], and meeting the dietary protein need from plants instead of animal-based foods can reduce the CVD risk possibly by evading the production of harmful metabolites, such as TMAO, from metabolism of choline and L-carnitine, which are abundant in animal-based foods [222]. A well-known strategy to modify the gut microbiota with diet is the use of prebiotics, which are indigestible food ingredients that support the growth of beneficial bacteria, such as Lactobacilli and Bifidobacteria species, while suppressing the growth of others, such as species from genera Enterobacteria, Clostridia, and Bacteroides [223]. In fact, high dietary fiber intake reduces the risk of inflammation and mortality in CKD patients [224]. In addition, consumption of an amylose-enriched diet has been shown to attenuate oxidative stress and inflammation, retard CKD progression, and markedly improve gut microbial dysbiosis in a rat model of CKD [225]. Moreover, beneficial bacteria in the gut microbiota can be supported by dietary supplementation of polyphenols [226], vitamin D [227], zinc [228], and iron [229], and some plant-derived essential oils [230] and fish oil [231] can suppress the growth of pathogenic species. Dietary L-arginine supplementation also strengthens gut mucosal immune barrier function [232]. Therefore, a balanced diet rich in plant-derived foods can promote a healthier gut flora.

Importantly, some medications can have favorable effects on the gut microbiota. First, oral hypoglycemic agents, such as metformin, can alter the gut microbiota in favor of beneficial species, such as *Akkermansia muciniphila*, which can thicken the mucus barrier [233], and Eubacterium while suppressing group Firmicutes in general [234]. Additionally, use of liraglutide and saxagliptin has been reported to improve the Lactobacillaceae level in the gut flora [235]. Furthermore, lubipristone can restore the Lactobacillaceae and Prevotella composition of the gut microbiota of mice with renal failure, thereby reducing the plasma levels of uremic toxins [236]. Emodin, which is the main ingredient of the Chinese medicine rhubarb, reduces the serum uremic toxin levels by suppressing the growth of Clostridium species and other harmful species while promoting the expansion of beneficial bacteria, such as Lactobacillus species [237].

Alpha-glucosidase inhibitors are other antidiabetic drugs that delay the digestion of carbohydrates, such as disaccharides and starch, in the small intestine. Acarbose administration in hyperlipidemic or T2D patients was shown to increase Lactobacillus and Bifidobacterium [238] as well as other SCFA-producing bacteria, such as Faecalibacterium and Prevotella [238]. Additionally, animal studies have shown that GLP-1 receptor agonists and dipeptidyl peptidase 4 inhibitors can alter the gut microbiota [239]. However, human studies in this context are not available at present. We also did not find any study showing the influence of sodium glucose co-transporter 2 inhibitors or meglitinides on the gut microbiota, and information is very scarce regarding sulfonylureas and thiazolidinediones.

Apart from hypoglycemic agents, a variety of drugs are used for the prevention of CKD and CVD. Recent evidence suggests that these drugs may affect the microbiota. Kjan et al. investigated the effects of atorvastatin treatment on the gut microbiota. The authors performed 16S rDNA amplicon sequencing to evaluate the gut bacterial communities of 15 untreated hypercholesterolemic patients (HPs) and 27 atorvastatin-treated hypercholesterolemic patients (At-HPs) compared with those of 19 healthy subjects (HSs). In total, 18 different phyla were identified in the study groups. An increase in relative abundance of Proteobacteria was observed in the HP group compared with that of the At-HP and HS groups. The atherosclerosis-associated genus Collinsella was found at a relatively higher abundance in the HP group. Anti-inflammation-associated bacteria (*Faecalibacterium prausnitzii*, *A. muciniphila*, and genus Oscillospira) were found in greater abundances, and the pro-inflammatory species *Desulfovibrio* sp. was observed at a decreased abundance in the drug-treated HP group compared with that of the untreated HP group. The relative abundances of *Bilophila wadsworthia* and *Bifidobacterium bifidum* (bile acid-associated species) were decreased in the At-HP group. These data suggest that atorvastatin treatment of patients with hypercholesterolemia may selectively restore the relative abundance of several dominant and functionally important taxa that are disrupted in HPs [240]. Simvastatin was also shown to affect the gut microbial composition and boost Lactobacillus populations [241]. Additionally, the relationship between antilipemic drugs and the microbiota is bi-directional instead of unidirectional. Costabile et al. showed that *Lactobacillus plantarum* ECGC 13110402 resulted in a statistically significant reduction in LDL cholesterol, a significant reduction in total cholesterol, a significant decrease in triglycerides, and an increase in high-density lipoprotein cholesterol during a 6–12-week period [242].

Regarding antihypertensive drugs, no specific study has investigated the effect of drugs on the gut microbiota. In

contrast, many studies have shown that probiotics may have antihypertensive effects [243].

These findings suggest that the gut microbiota can be modified by some medications. Therefore, an investigation of the effects of currently used medications on the gut microbiota is reasonable, and those with the greatest benefits on the gut microbiota may even be chosen as adjunct therapies for insufficient prebiotic/probiotic treatments.

Interestingly, not only diet and medications but also the physical activity level can alter the gut microbiota composition. There is mounting evidence that exercise supports the growth of beneficial species and enriches the diversity of the gut microbiota, thereby improving health [244]. Therefore, regular exercise keeps not only the body but also the gut microbiota fit.

The role of the gut microbiota in the central nervous system (CNS; e.g., appetite and the reward system) is also worth mentioning. Energy homeostasis is tightly regulated by the CNS, which responds to nervous and circulating inputs to adapt food intake and energy expenditure. The rewarding and motivational aspects of food are tightly dependent on DA release in the mesocorticolimbic system. Accumulating evidence indicates that manipulating the microbiota–gut–brain axis through prebiotic supplementation can have beneficial impacts of the host's appetite and body weight [245].

Indeed, microbial metabolites were suggested to affect host metabolism through a variety of pathways, one of which was affecting central appetite pathways integrating the host energy status [246]. Bacterial strains were also hypothesized to provide a potent therapeutic for neurological diseases by producing or altering neurochemicals and could most likely play a pivotal role in influencing appetite and energy metabolism via modulation of the CNS [247].

Various studies have shown that dietary prebiotics, such as the soluble fibers fructo-oligosaccharides, which represents selectively fermented compounds, promote changes in the activity and composition of the gut microbiota that are associated with reduced appetite [248]. A recent study showed that weight gain in anorexia nervosa was related to dysregulation of appetite and decreased gut microbial diversity [249].

Administration of *Citrobacter rodentium* to mice increased anxiety-like behaviors [93] and *B. longum* normalized anxiety-like behavior following nematode-induced gastrointestinal inflammation [92]. Clinical studies have also suggested that ingestion of probiotics may decrease anxiety and depression [250]. This evidence suggests that the gut microbiota affects higher CNS functions and behavior, but large clinical trials are needed to evaluate the efficacy of antibiotic as well as probiotic ("psychobiotic") therapies.

Lastly, other than the gut microbiota, its products, such as the uremic toxins and LPS, can be targeted to prevent the development and progression of CKD and CVD. For example, adsorption of uremic toxins by AST-120 [251], blocking metabolic pathways leading to the production of the uremic toxins TMAO and IS with TMA inhibitor [252] and inhibition of hepatic sulfation of indoxyl [253] are among the strategies being developed to reduce serum uremic toxin levels and attenuate consequent inflammation [254]. Additionally, sevelamer, which is a large cationic polymer phosphate binder, has been shown to adsorb and remove LPS in HD patients [251]. Therefore, investigation of the metabolism of toxins produced by bacteria and development of new methods to prevent the deleterious effects of bacterial metabolic waste products and endotoxins are important avenues for the prevention and treatment of CKD, CVD, and other chronic inflammatory diseases.

Conclusion

The intestines, cardiovascular system, and kidneys are intimately engaged with each other, and their crosstalk plays a decisive role in the development of two of the most common and important chronic diseases: CKD and CVD. The gut microbiota and its effects on the host inflammatory status are key components of this crosstalk. Therefore, deciphering the role of the gut microbiota in gut–cardiovascular system–kidney crosstalk will create novel opportunities for the prevention and treatment of many previously undertreated conditions, including CVD and CKD.

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