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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	Enterobacteriaceae, 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, Pseudobutyrvibrio, Ruminococcaceae
Diabetic nephropathy ^a	Type 1 DM: Bacteroides, Blautia, Rikenellaceae, Ruminococcus, Streptococcus, <i>Clostridium perfringens</i> , Veillonella, Fusobacteria, (Leptotrichia) Type 2 DM: Escherichia, Prevotella, <i>Clostridium boltea</i> , <i>Clostridium symbiosum</i> , <i>Clostridium ramosum</i> , <i>Clostridium hathewayi</i> , Betaproteobacteria, Desulfovibrio	Type 1 DM: Lactobacillus, Bifidobacterium, Prevotella, Staphylococcus, Lachnospiraceae, Veillonellaceae, <i>Coprococcus eutactus</i> , <i>Dialister invisus</i> , <i>Roseburia faecis</i> , <i>Faecalibacterium prausnitzii</i> , <i>Clostridium clostridioforme</i> , <i>Blautia coccoides</i> , Pseudobutyrvibrio, Akkermansia muciniphila ^b Type 2 DM: Bifidobacterium, <i>Eubacterium rectale</i> , Faecalibacterium, <i>Roseburia intestinalis</i> , Clostridiales, Lactobacillus, <i>Akkermansia muciniphila</i> ^b (Verrucomicrobiaceae), Streptococcus

^aSince 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

^bAkkermansia 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*, *Coprococcus* [43] were found to be increased while *Faecalibacterium*, *Oscillibacter*, *Roseburia*, *Bifidobacterium*, *Coprococcus*, *Clostridium*, *Butyrivibrio*, *Pseudobutyribacterium*, 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 H₂S [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 Faecalibacterium, Oscillibacter, Roseburia, Bifidobacterium, Coprococcus, Clostridium, Butyrivibrio, Pseudobutyrvibrio, and Ruminococcaceae were decreased in hypertensive subjects [Ref. 43]
- The observed changes in the composition of the gut microbiota 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, Pseudobutyrvibrio, 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 (Pseudobutyrvibrio [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 now, 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, Pseudobutyrvibrio, 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 microbiota 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 gausvreauii* 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 ± 10 years old; 57% men; eGFR = 24 ± 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 lubiprostone [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.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Lozupone CA, Stombaugh JJ, Gordon JJ, Jansson JK, Knight R (2012) Diversity, stability and resilience of the human gut microbiota. *Nature* 489:220–230
2. Savage DC (1977) Microbial ecology of the gastrointestinal tract. *Annu Rev Microbiol* 31:107–133
3. Yoshifuji A, Wakino S, Irie J, Tajima T, Hasegawa K, Kanda T, Tokuyama H, Hayashi K, Itoh H (2016) Gut Lactobacillus protects against the progression of renal damage by modulating the gut environment in rats. *Nephrol Dial Transplant* 31:401–412
4. Wen L, Duffy A (2017) Factors influencing the gut microbiota, inflammation, and type 2 diabetes. *J Nutr* 147:1468s–1475s
5. Roesch LF, Lorca GL, Casella G, Giongo A, Naranjo A, Pionzio AM, Li N, Mai V, Wasserfall CH, Schatz D, Atkinson MA, Neu J, Triplett EW (2009) Culture-independent identification of gut bacteria correlated with the onset of diabetes in a rat model. *ISME J* 3:536–548
6. Yang T, Santisteban MM, Rodriguez V, Li E, Ahmari N, Carvajal JM, Zadeh M, Gong M, Qi Y, Zubcevic J, Sahay B, Pepine CJ, Raizada MK, Mohamadzaheh M (2015) Gut dysbiosis is linked to hypertension. *Hypertension* 65:1331–1340
7. Khoury T, Tzuket K, Abel R, Abu Rmeileh A, Levi R, Ilan Y (2017) The gut-kidney axis in chronic renal failure: a new potential target for therapy. *Hemodial Int* 21:323–334
8. Amdur RL, Feldman HI, Gupta J, Yang W, Kanetsky P, Shlipak M, Rahman M, Lash JP, Townsend RR, Ojo A, Roy-Chaudhury A, Go AS, Joffe M, He J, Balakrishnan VS, Kimmel PL, Kusek

- JW, Raj DS (2016) Inflammation and progression of CKD: the CRIC Study. *Clin J Am Soc Nephrol* 11:1546–1556
9. Silverstein DM (2009) Inflammation in chronic kidney disease: role in the progression of renal and cardiovascular disease. *Pediatr Nephrol* 24:1445–1452
 10. Lewis B, Mukewar S, Lopez R, Brzezinski A, Hall P, Shen B (2013) Frequency and risk factors of renal insufficiency in inflammatory bowel disease inpatients. *Inflamm Bowel Dis* 19:1846–1851
 11. Casén C, Vebø HC, Sekelja M, Hegge FT, Karlsson MK, Cierniejewska E, Dzankovic S, Frøyland C, Nestestog R, Engstrand L, Munkholm P, Nielsen OH, Rogler G, Simrén M, Öhman L, Vatn MH, Rudi K (2015) Deviations in human gut microbiota: a novel diagnostic test for determining dysbiosis in patients with IBS or IBD. *Aliment Pharmacol Ther* 42:71–83
 12. Vaziri ND, Wong J, Pahl M, Piceno YM, Yuan J, DeSantis TZ, Ni Z, Nguyen TH, Andersen GL (2013) Chronic kidney disease alters intestinal microbial flora. *Kidney Int* 83:308–315
 13. Mahmoodpoor F, Rahbar Saadat Y, Barzegari A, Ardalan M, Zununi Vahed S (2017) The impact of gut microbiota on kidney function and pathogenesis. *Biomed Pharmacother* 93:412–419
 14. Jakobsson HE, Rodriguez-Pineiro AM, Schutte A, Ermund A, Boysen P, Bemark M, Sommer F, Backhed F, Hansson GC, Johansson ME (2015) The composition of the gut microbiota shapes the colon mucus barrier. *EMBO Rep* 16:164–177
 15. Omenetti S, Pizarro TT (2015) The Treg/Th17 axis: a dynamic balance regulated by the gut microbiome. *Front Immunol* 6:639
 16. Shi K, Wang F, Jiang H, Liu H, Wei M, Wang Z, Xie L (2014) Gut bacterial translocation may aggravate microinflammation in hemodialysis patients. *Dig Dis Sci* 59:2109–2117
 17. Poveda J, Sanchez-Nino MD, Glorieux G, Sanz AB, Egidio J, Vanholder R, Ortiz A (2014) p-Cresyl sulphate has pro-inflammatory and cytotoxic actions on human proximal tubular epithelial cells. *Nephrol Dial Transplant* 29:56–64
 18. Wong J, Piceno YM, DeSantis TZ, Pahl M, Andersen GL, Vaziri ND (2014) Expansion of urease- and uricase-containing, indole- and p-cresol-forming and contraction of short-chain fatty acid-producing intestinal microbiota in ESRD. *Am J Nephrol* 39:230–237
 19. Ridlon JM, Kang DJ, Hylemon PB (2006) Bile salt biotransformations by human intestinal bacteria. *J Lipid Res* 47:241–259
 20. Truong LD, Trostel J, Garcia GE (2015) Absence of nicotinic acetylcholine receptor $\alpha 7$ subunit amplifies inflammation and accelerates onset of fibrosis: an inflammatory kidney model. *FASEB J* 29:3558–3570
 21. Ohland CL, Macnaughton WK (2010) Probiotic bacteria and intestinal epithelial barrier function. *Am J Physiol Gastrointest Liver Physiol* 298:G807–G819
 22. Barrett E, Ross RP, O'Toole PW, Fitzgerald GF, Stanton C (2012) gamma-Aminobutyric acid production by culturable bacteria from the human intestine. *J Appl Microbiol* 113:411–417
 23. Sobko T, Huang L, Midtvedt T, Norin E, Gustafsson LE, Norman M, Jansson EA, Lundberg JO (2006) Generation of NO by probiotic bacteria in the gastrointestinal tract. *Free Radic Biol Med* 41:985–991
 24. de Andrade JAA, Gayer CRM, Nogueira NPA, Paes MC, Bastos V, Neto J, Alves SC Jr, Coelho RM, da Cunha M, Gomes RN, Aguilá MB, Mandarim-de-Lacerda CA, Bozza PT, da Cunha S (2014) The effect of thiamine deficiency on inflammation, oxidative stress and cellular migration in an experimental model of sepsis. *J Inflamm (Lond)* 11:11
 25. Everard A, Cani PD (2014) Gut microbiota and GLP-1. *Rev Endocr Metab Disord* 15:189–196
 26. Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, Bienenstock J, Cryan JF (2011) Ingestion of *Lactobacillus* strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proc Natl Acad Sci USA* 108:16050–16055
 27. Vaziri ND, Zhao YY, Pahl MV (2016) Altered intestinal microbial flora and impaired epithelial barrier structure and function in CKD: the nature, mechanisms, consequences and potential treatment. *Nephrol Dial Transplant* 31:737–746
 28. Uy N, Graf L, Lemley K, Kaskel F (2015) Effects of gluten-free, dairy-free diet on childhood nephrotic syndrome and gut microbiota. *Pediatr Res* 77:252–255
 29. Mu Q, Zhang H, Liao X, Lin K, Liu H, Edwards MR, Ahmed SA, Yuan R, Li L, Cecere TE, Branson DB, Kirby JL, Goswami P, Leeth CM, Read KA, Oestreich KJ, Vieson MD, Reilly CM, Luo XM (2017) Control of lupus nephritis by changes of gut microbiota. *Microbiome* 5:73
 30. Reigstad CS, Lunden GO, Felin J, Backhed F (2009) Regulation of serum amyloid A3 (SAA3) in mouse colonic epithelium and adipose tissue by the intestinal microbiota. *PLoS ONE* 4:e5842
 31. Barcenilla A, Pryde SE, Martin JC, Duncan SH, Stewart CS, Henderson C, Flint HJ (2000) Phylogenetic relationships of butyrate-producing bacteria from the human gut. *Appl Environ Microbiol* 66:1654–1661
 32. Li J, Zhao F, Wang Y, Chen J, Tao J, Tian G, Wu S, Liu W, Cui Q, Geng B, Zhang W, Weldon R, Auguste K, Yang L, Liu X, Chen L, Yang X, Zhu B, Cai J (2017) Gut microbiota dysbiosis contributes to the development of hypertension. *Microbiome* 5:14
 33. Pushpanathan P, Srikanth P, Seshadri KG, Selvarajan S, Pitani RS, Kumar TD, Janarthanan R (2016) Gut microbiota in type 2 diabetes individuals and correlation with monocyte chemoattractant protein1 and interferon gamma from patients attending a Tertiary Care Centre in Chennai, India. *Indian J Endocrinol Metab* 20:523–530
 34. Kohn FR, Kung AH (1995) Role of endotoxin in acute inflammation induced by gram-negative bacteria: specific inhibition of lipopolysaccharide-mediated responses with an amino-terminal fragment of bactericidal/permeability-increasing protein. *Infect Immun* 63:333–339
 35. Koeth RA, Wang Z, Levison BS, Buffa JA, Org E, Sheehy BT, Britt EB, Fu X, Wu Y, Li L, Smith JD, DiDonato JA, Chen J, Li H, Wu GD, Lewis JD, Warrier M, Brown JM, Krauss RM, Tang WH, Bushman FD, Lusis AJ, Hazen SL (2013) Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat Med* 19:576–585
 36. Atarashi K, Tanoue T, Shima T, Imaoka A, Kuwahara T, Momose Y, Cheng G, Yamasaki S, Saito T, Ohba Y, Taniguchi T, Takeda K, Hori S, Ivanov II, Umesaki Y, Itoh K, Honda K (2011) Induction of colonic regulatory T cells by indigenous *Clostridium* species. *Science* 331:337–341
 37. Sun CY, Hsu HH, Wu MS (2013) p-Cresol sulfate and indoxyl sulfate induce similar cellular inflammatory gene expressions in cultured proximal renal tubular cells. *Nephrol Dial Transplant* 28:70–78
 38. Tang WH, Wang Z, Kennedy DJ, Wu Y, Buffa JA, Agatista-Boyle B, Li XS, Levison BS, Hazen SL (2015) Gut microbiota-dependent trimethylamine N-oxide (TMAO) pathway contributes to both development of renal insufficiency and mortality risk in chronic kidney disease. *Circ Res* 116:448–455
 39. Toyohara T, Suzuki T, Morimoto R, Akiyama Y, Souma T, Shiwaku HO, Takeuchi Y, Mishima E, Abe M, Tanemoto M, Masuda S, Kawano H, Maemura K, Nakayama M, Sato H, Mikkaichi T, Yamaguchi H, Fukui S, Fukumoto Y, Shimokawa H, Inui K-i, Terasaki T, Goto J, Ito S, Hishinuma T, Rubera I, Tauc M, Fujii-Kuriyama Y, Yabuuchi H, Moriyama Y, Soga T, Abe T (2009) SLCO4C1 transporter eliminates uremic toxins and attenuates hypertension and renal inflammation. *J Am Soc Nephrol* 20:2546–2555

40. Okada K, Takahashi Y, Okawa E, Onishi Y, Hagi C, Aoki K, Shibahara H, Higuchi T, Nagura Y, Kanmatsuse K, Takahashi S (2001) Relationship between insulin resistance and uremic toxins in the gastrointestinal tract. *Nephron* 88:384–386
41. Bansal T, Alaniz RC, Wood TK, Jayaraman A (2010) The bacterial signal indole increases epithelial-cell tight-junction resistance and attenuates indicators of inflammation. *Proc Natl Acad Sci USA* 107:228–233
42. Wong X, Carrasco-Pozo C, Escobar E, Navarrete P, Blachier F, Andriamihaja M, Lan A, Tomé D, Cires MJ, Pastene E, Gotteland M (2016) Deleterious effect of p-cresol on human colonic epithelial cells prevented by proanthocyanidin-containing polyphenol extracts from fruits and proanthocyanidin bacterial metabolites. *J Agric Food Chem* 64:3574–3583
43. Durgan DJ, Ganesh BP, Cope JL, Ajami NJ, Phillips SC, Petrosino JF, Hollister EB, Bryan RM (2016) Role of the gut microbiome in obstructive sleep apnea-induced hypertension. *Hypertension* 67:469–474
44. Adnan S, Nelson JW, Ajami NJ, Venna VR, Petrosino JF, Bryan RM, Durgan DJ (2017) Alterations in the gut microbiota can elicit hypertension in rats. *Physiol Genom* 49:96
45. Santisteban MM, Qi Y, Zubcevic J, Kim S, Yang T, Shenoy V, Cole-Jeffrey CT, Lobaton GO, Stewart DC, Rubiano A, Simmons CS, Garcia-Pereira F, Johnson RD, Pepine CJ, Raizada MK (2017) Hypertension-linked pathophysiological alterations in the gut. *Circ Res* 120:312–323
46. Griffiths EA, Duffy LC, Schanbacher FL, Qiao H, Dryja D, Leavens A, Rossman J, Rich G, Dirienzo D, Ogra PL (2004) In vivo effects of bifidobacteria and lactoferrin on gut endotoxin concentration and mucosal immunity in Balb/c mice. *Dig Dis Sci* 49:579–589
47. Natarajan N, Hori D, Flavahan S, Steppan J, Flavahan NA, Berkowitz DE, Pluznick JL (2016) Microbial short chain fatty acid metabolites lower blood pressure via endothelial G-protein coupled receptor 41. *Physiol Genom*. <https://doi.org/10.1152/physiolgenomics.00089.2016>
48. Juraschek SP, Bower JK, Selvin E, Subash Shantha GP, Hoo-geveen RC, Ballantyne CM, Young JH (2015) Plasma lactate and incident hypertension in the atherosclerosis risk in communities study. *Am J Hypertens* 28:216–224
49. Saemann MD, Bohmig GA, Osterreicher CH, Burtscher H, Parolini O, Diakos C, Stockl J, Horl WH, Zlabinger GJ (2000) Anti-inflammatory effects of sodium butyrate on human monocytes: potent inhibition of IL-12 and up-regulation of IL-10 production. *FASEB J* 14:2380–2382
50. Basu A, Charkoudian N, Schrage W, Rizza RA, Basu R, Joyner MJ (2007) Beneficial effects of GLP-1 on endothelial function in humans: dampening by glyburide but not by glimepiride. *Am J Physiol Endocrinol Metab* 293:E1289–E1295
51. Ito WD, Lund N, Sager H, Becker W, Wenzel U (2015) Differential impact of diabetes mellitus type II and arterial hypertension on collateral artery growth and concomitant macrophage accumulation. *Vasa* 44:31–41
52. Liu KX, Chen SQ, Huang WQ, Li YS, Irwin MG, Xia Z (2008) Propofol pretreatment reduces ceramide production and attenuates intestinal mucosal apoptosis induced by intestinal ischemia/reperfusion in rats. *Anesth Analg* 107:1884–1891
53. Wang F, Li Q, He Q, Geng Y, Tang C, Wang C, Li J (2013) Temporal variations of the ileal microbiota in intestinal ischemia and reperfusion. *Shock* 39:96–103
54. Peng J, Narasimhan S, Marchesi JR, Benson A, Wong FS, Wen L (2014) Long term effect of gut microbiota transfer on diabetes development. *J Autoimmun* 53:85–94
55. Vrieze A, Van Nood E, Holleman F, Salojarvi J, Kootte RS, Bartelsman JF, Dallinga-Thie GM, Ackermans MT, Serlie MJ, Oozeer R, Derrien M, Druesne A, Van Hylckama Vlieg JE, Bloks VW, Groen AK, Heilig HG, Zoetendal EG, Strees ES, de Vos WM, Hoekstra JB, Nieuwdorp M (2012) Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology* 143:913–916.e917
56. Bosi E, Molteni L, Radaelli MG, Folini L, Fermo I, Bazzigaluppi E, Piemonti L, Pastore MR, Paroni R (2006) Increased intestinal permeability precedes clinical onset of type 1 diabetes. *Diabetologia* 49:2824–2827
57. Cani PD, Possemiers S, Van de Wiele T, Guiot Y, Everard A, Rottier O, Geurts L, Naslain D, Neyrinck A, Lambert DM, Muccioli GG, Delzenne NM (2009) Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. *Gut* 58:1091–1103
58. Kopecký J, Zorec M, Mrazek J, Kobayashi Y, Marinsek-Logar R (2003) *Butyrivibrio hungatei* sp. nov. and *Pseudobutyrvibrio xylanivorans* sp. nov., butyrate-producing bacteria from the rumen. *Int J Syst Evol Microbiol* 53:201–209
59. Qin J, Li Y, Cai Z, Li S, Zhu J, Zhang F, Liang S, Zhang W, Guan Y, Shen D, Peng Y, Zhang D, Jie Z, Wu W, Qin Y, Xue W, Li J, Han L, Lu D, Wu P, Dai Y, Sun X, Li Z, Tang A, Zhong S, Li X, Chen W, Xu R, Wang M, Feng Q, Gong M, Yu J, Zhang Y, Zhang M, Hansen T, Sanchez G, Raes J, Falony G, Okuda S, Almeida M, LeChatelier E, Renault P, Pons N, Batto J-M, Zhang Z, Chen H, Yang R, Zheng W, Li S, Yang H, Wang J, Ehrlich SD, Nielsen R, Pedersen O, Kristiansen K, Wang J (2012) A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature* 490:55–60
60. Brown CT, Davis-Richardson AG, Giongo A, Gano KA, Crabb DB, Mukherjee N, Casella G, Drew JC, Ilonen J, Knip M, Hyöty H, Veijola R, Simell T, Simell O, Neu J, Wasserfall CH, Schatz D, Atkinson MA, Triplett EW (2011) Gut microbiome metagenomics analysis suggests a functional model for the development of autoimmunity for type 1 diabetes. *PLoS ONE* 6:e25792
61. Hague A, Butt AJ, Paraskeva C (1996) The role of butyrate in human colonic epithelial cells: an energy source or inducer of differentiation and apoptosis? *Proc Nutr Soc* 55:937–943
62. Peng L, Li Z-R, Green RS, Holzman IR, Lin J (2009) Butyrate Enhances the intestinal barrier by facilitating tight junction assembly via activation of AMP-activated protein kinase in caco-2 cell monolayers. *J Nutr* 139:1619–1625
63. Burger-van Paassen N, Vincent A, Puiman PJ, van der Sluis M, Bouma J, Boehm G, van Goudoever JB, van Seuningen I, Renes IB (2009) The regulation of intestinal mucin MUC2 expression by short-chain fatty acids: implications for epithelial protection. *Biochem J* 420:211–219
64. Deplancke B, Vidal O, Ganessunker D, Donovan SM, Mackie RI, Gaskins HR (2002) Selective growth of mucolytic bacteria including *Clostridium perfringens* in a neonatal piglet model of total parenteral nutrition. *Am J Clin Nutr* 76:1117–1125
65. Wright DP, Knight CG, Parkar SG, Christie DL, Robertson AM (2000) Cloning of a mucin-desulfating sulfatase gene from prevotella strain RS2 and its expression using a bacteroides recombinant system. *J Bacteriol* 182:3002–3007
66. Smedley JG, Fisher DJ, Sayeed S, Chakrabarti G, McClane BA (2005) The enteric toxins of *Clostridium perfringens*. Reviews of physiology, biochemistry and pharmacology. Springer, Berlin, pp 183–204
67. Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, Neyrinck AM, Fava F, Tuohy KM, Chabo C, Waget A, Delmée E, Cousin B, Sulpice T, Chamontin B, Ferrières J, Tanti J-F, Gibson GR, Casteilla L, Delzenne NM, Alessi MC, Burcelin R (2007) Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes* 56:1761

68. Nymark M, Pussinen PJ, Tuomainen AM, Forsblom C, Groop P-H, Lehto M, On behalf of the FinnDiane Study Group (2009) Serum lipopolysaccharide activity is associated with the progression of kidney disease in Finnish patients with type 1 diabetes. *Diabetes Care* 32:1689–1693
69. Tai N, Peng J, Liu F, Gulden E, Hu Y, Zhang X, Chen L, Wong FS, Wen L (2016) Microbial antigen mimics activate diabetogenic CD8 T cells in NOD mice. *J Exp Med* 213:2129–2146
70. Dolpady J, Sorini C, Di Pietro C, Cosorich I, Ferrarese R, Saita D, Clementi M, Canducci F, Falcone M (2016) Oral probiotic VSL#3 prevents autoimmune diabetes by modulating microbiota and promoting indoleamine 2,3-dioxygenase-enriched tolerogenic intestinal environment. *J Diabetes Res* 2016:7569431
71. Round JL, Lee SM, Li J, Tran G, Jabri B, Chatila TA, Mazmanian SK (2011) The Toll-like receptor pathway establishes commensal gut colonization. *Science* 332:974–977
72. Furusawa Y, Obata Y, Fukuda S, Endo TA, Nakato G, Takahashi D, Nakanishi Y, Uetake C, Kato K, Kato T, Takahashi M, Fukuda NN, Murakami S, Miyauchi E, Hino S, Atarashi K, Onawa S, Fujimura Y, Lockett T, Clarke JM, Topping DL, Tomita M, Hori S, Ohara O, Morita T, Koseki H, Kikuchi J, Honda K, Hase K, Ohno H (2013) Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature* 504:446–450
73. LeBlanc JG, Laino JE, del Valle MJ, Vannini V, van Sinderen D, Taranto MP, de Valdez GF, de Giori GS, Sesma F (2011) B-group vitamin production by lactic acid bacteria—current knowledge and potential applications. *J Appl Microbiol* 111:1297–1309
74. Jayashree S, Jayaraman K, Kalaichelvan G (2010) Isolation, screening and characterization of riboflavin producing lactic acid bacteria from Katpadi, Vellore district. *Recent Res Sci Technol* 2:83–88
75. Kjer-Nielsen L, Patel O, Corbett AJ, Le Nours J, Meehan B, Liu L, Bhati M, Chen Z, Kostenko L, Reantragoon R, Williamson NA, Purcell AW, Dudek NL, McConville MJ, O'Hair RAJ, Khairallah GN, Godfrey DI, Fairlie DP, Rossjohn J, McCluskey J (2012) MR1 presents microbial vitamin B metabolites to MAIT cells. *Nature* 491:717–723
76. Ruijing X, Mengjun W, Xiaoling Z, Shu P, Mei W, Yingcheng Z, Yuling H, Jinquan T (2012) α 33 + MAIT cells play a protective role in TNBS induced intestinal inflammation. *Hepato-gastroenterology* 59:762–767
77. Qiao Y-c, Shen J, He L, Hong X-z, Tian F, Pan Y-h, Liang L, Zhang X-x, Zhao H-l (2016) Changes of regulatory T cells and of proinflammatory and immunosuppressive cytokines in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. *J Diabetes Res* 2016:3694957
78. Badami E, Sorini C, Coccia M, Uselli V, Molteni L, Bolla AM, Scavini M, Mariani A, King C, Bosi E, Falcone M (2011) Defective differentiation of regulatory FoxP3(+) T cells by small-intestinal dendritic cells in patients with type 1 diabetes. *Diabetes* 60:2120–2124
79. Wen L, Wong FS (2017) Dietary short-chain fatty acids protect against type 1 diabetes. *Nat Immunol* 18:484–486
80. Shi G, Sun C, Gu W, Yang M, Zhang X, Zhai N, Lu Y, Zhang Z, Shou P, Zhang Z, Ning G (2014) Free fatty acid receptor 2, a candidate target for type 1 diabetes, induces cell apoptosis through ERK signaling. *J Mol Endocrinol* 53:367–380
81. McNelis JC, Lee YS, Mayoral R, van der Kant R, Johnson AM, Wollam J, Olefsky JM (2015) GPR43 potentiates beta-cell function in obesity. *Diabetes* 64:3203–3217
82. Venter CS, Vorster HH, Cummings JH (1990) Effects of dietary propionate on carbohydrate and lipid metabolism in healthy volunteers. *Am J Gastroenterol* 85:549–553
83. Villa SR, Priyadarshini M, Fuller MH, Bhardwaj T, Brodsky MR, Angueira AR, Mosser RE, Carboneau BA, Tersey SA, Mancebo H, Gilchrist A, Mirmira RG, Gannon M, Layden BT (2016) Loss of free fatty acid receptor 2 leads to impaired islet mass and beta cell survival. *Sci Rep* 6:28159
84. Tolhurst G, Heffron H, Lam YS, Parker HE, Habib AM, Diakogiannaki E, Cameron J, Grosse J, Reimann F, Gribble FM (2012) Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein-coupled receptor FFAR2. *Diabetes* 61:364–371
85. Creutzfeldt WO, Kleine N, Willms B, Orskov C, Holst JJ, Nauck MA (1996) Glucagonostatic actions and reduction of fasting hyperglycemia by exogenous glucagon-like peptide I (7–36) amide in type I diabetic patients. *Diabetes Care* 19:580–586
86. Grigoropoulou P, Eleftheriadou I, Zoupas C, Diamanti-Kandarakis E, Tentolouris N (2013) Incretin-based therapies for type 2 diabetes mellitus: effects on insulin resistance. *Curr Diabetes Rev* 9:412–417
87. Holz GG (2004) Epac: a new cAMP-binding protein in support of glucagon-like peptide-1 receptor-mediated signal transduction in the pancreatic beta-cell. *Diabetes* 53:5–13
88. Cobianchi L, Fornoni A, Pileggi A, Molano RD, Sanabria NY, Gonzalez-Quintana J, Bocca N, Marzorati S, Zahr E, Hogan AR, Ricordi C, Inverardi L (2008) Riboflavin inhibits IL-6 expression and p38 activation in islet cells. *Cell Transplant* 17:559–566
89. Tian J, Lu Y, Zhang H, Chau CH, Dang HN, Kaufman DL (2004) Gamma-aminobutyric acid inhibits T cell autoimmunity and the development of inflammatory responses in a mouse type 1 diabetes model. *J Immunol* 173:5298–5304
90. Marques TM, Patterson E, Wall R, O'Sullivan O, Fitzgerald GF, Cotter PD, Dinan TG, Cryan JF, Ross RP, Stanton C (2016) Influence of GABA and GABA-producing *Lactobacillus brevis* DPC 6108 on the development of diabetes in a streptozotocin rat model. *Benef Microbes* 7:409–420
91. Joshi A, Woodman OL (2012) Increased nitric oxide activity compensates for increased oxidative stress to maintain endothelial function in rat aorta in early type 1 diabetes. *Naunyn-Schmiedeberg's Arch Pharmacol* 385:1083–1094
92. Aldahmash BA, El-Nagar DM, Ibrahim KE (2016) Attenuation of hepatotoxicity and oxidative stress in diabetes STZ-induced type 1 by biotin in Swiss albino mice. *Saudi J Biol Sci* 23:311–317
93. Peña AS, Maftai O, Dowling K, Gent R, Wiltshire E, MacKenzie K, Couper J (2013) Folate fortification and supplementation do not provide vascular health benefits in type 1 diabetes. *J Pediatr* 163:255–260
94. Wang XX, Jiang T, Shen Y, Caldas Y, Miyazaki-Anzai S, Santamaria H, Urbanek C, Solis N, Scherzer P, Lewis L, Gonzalez FJ, Adorini L, Pruzanski M, Kopp JB, Verlander JW, Levi M (2010) Diabetic nephropathy is accelerated by farnesoid X receptor deficiency and inhibited by farnesoid X receptor activation in a type 1 diabetes model. *Diabetes* 59:2916–2927
95. Zhu C, Fuchs CD, Halilbasic E, Trauner M (2016) Bile acids in regulation of inflammation and immunity: friend or foe? *Clin Exp Rheumatol* 34:25–31
96. Moynes DM, Lucas GH, Beyak MJ, Lomax AE (2014) Effects of inflammation on the innervation of the colon. *Toxicol Pathol* 42:111–117
97. Bruce DG, Chisholm DJ, Storlien LH, Kraegen EW, Smythe GA (1992) The effects of sympathetic nervous system activation and psychological stress on glucose metabolism and blood pressure in subjects with type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 35:835–843
98. Beilharz JE, Kaakoush NO, Maniam J, Morris MJ (2016) The effect of short-term exposure to energy-matched diets enriched in fat or sugar on memory, gut microbiota and markers of brain inflammation and plasticity. *Brain Behav Immun* 57:304–313
99. Watkins CC, Sawa A, Jaffrey S, Blackshaw S, Barrow RK, Snyder SH, Ferris CD (2000) Insulin restores neuronal nitric oxide

- synthase expression and function that is lost in diabetic gastropathy. *J Clin Invest* 106:373–384
100. Ordog T, Takayama I, Cheung WK, Ward SM, Sanders KM (2000) Remodeling of networks of interstitial cells of cajal in a murine model of diabetic gastroparesis. *Diabetes* 49:1731–1739
 101. Virally-Monod M, Tiélmans D, Kevorkian JP, Bouhnik Y, Flourie B, Porokhov B, Ajzenberg C, Warnet A, Guillausseau PJ (1998) Chronic diarrhoea and diabetes mellitus: prevalence of small intestinal bacterial overgrowth. *Diabetes Metab* 24:530–536
 102. Wang L, Li P, Tang Z, Yan X, Feng B (2016) Structural modulation of the gut microbiota and the relationship with body weight: compared evaluation of liraglutide and saxagliptin treatment. *Sci Rep* 6:33251
 103. Sun G, Yin Z, Liu N, Bian X, Yu R, Su X, Zhang B, Wang Y (2017) Gut microbial metabolite TMAO contributes to renal dysfunction in a mouse model of diet-induced obesity. *Biochem Biophys Res Commun* 493:964–970
 104. Wu B, Jiang H, He Q, Wang M, Xue J, Liu H, Shi K, Wei M, Liang S, Zhang L (2017) Liquid chromatography/mass spectrometry reveals the effect of lactobacillus treatment on the faecal metabolite profile of rats with chronic renal failure. *Nephron* 135:156–166
 105. Marques FZ, Nelson E, Chu PY, Horlock D, Fiedler A, Ziemann M, Tan JK, Kuruppu S, Rajapakse NW, El-Osta A, Mackay CR, Kaye DM (2017) High-fiber diet and acetate supplementation change the gut microbiota and prevent the development of hypertension and heart failure in hypertensive mice. *Circulation* 135:964–977
 106. Stewart DC, Rubiano A, Santisteban MM, Shenoy V, Qi Y, Pepine CJ, Raizada MK, Simmons CS (2016) Hypertension-linked mechanical changes of rat gut. *Acta Biomater* 45:296–302
 107. Li X, Wang E, Yin B, Fang D, Chen P, Wang G, Zhao J, Zhang H, Chen W (2017) Effects of *Lactobacillus casei* CCFM419 on insulin resistance and gut microbiota in type 2 diabetic mice. *Benef Microbes* 8:421–432
 108. Singh S, Sharma RK, Malhotra S, Pothuraju R, Shandilya UK (2017) *Lactobacillus rhamnosus* NCDC17 ameliorates type-2 diabetes by improving gut function, oxidative stress and inflammation in high-fat-diet fed and streptozotocintreated rats. *Benef Microbes* 8:243–255
 109. Yacoub R, Nugent M, Cai W, Nadkarni GN, Chaves LD, Abyad S, Honan AM, Thomas SA, Zheng W, Valiyaparambil SA, Bryniarski MA, Sun Y, Buck M, Genco RJ, Quigg RJ, He JC, Uribarri J (2017) Advanced glycation end products dietary restriction effects on bacterial gut microbiota in peritoneal dialysis patients; a randomized open label controlled trial. *PLoS ONE* 12:e0184789
 110. Rossi M, Johnson DW, Morrison M, Pascoe EM, Coombes JS, Forbes JM, Szeto CC, McWhinney BC, Ungerer JP, Campbell KL (2016) Synbiotics easing renal failure by improving gut microbiology (SYNERGY): a randomized trial. *Clin J Am Soc Nephrol* 11:223–231
 111. Fangmann D, Theismann EM, Turk K, Schulte DM, Relling I, Hartmann K, Keppler JK, Knipp JR, Rehman A, Heinsen FA, Franke A, Lenk L, Freitag-Wolf S, Appel E, Gorb S, Brenner C, Seegert D, Waetzig GH, Rosenstiel P, Schreiber S, Schwarz K, Laudes M (2017) Targeted microbiome intervention by micro-encapsulated delayed-release niacin beneficially affects insulin sensitivity in humans. *Diabetes Care*. <https://doi.org/10.2337/dc17-1967>
 112. Soleimani A, Zarrati Mojarrad M, Bahmani F, Taghizadeh M, Ramezani M, Tajabadi-Ebrahimi M, Jafari P, Esmailzadeh A, Asemi Z (2017) Probiotic supplementation in diabetic hemodialysis patients has beneficial metabolic effects. *Kidney Int* 91:435–442
 113. Balfego M, Canivell S, Hanzu FA, Sala-Vila A, Martinez-Medina M, Murillo S, Mur T, Ruano EG, Linares F, Porras N, Valladares S, Fontalba M, Roura E, Novials A, Hernandez C, Aranda G, Siso-Almirall A, Rojo-Martinez G, Simo R, Gomis R (2016) Effects of sardine-enriched diet on metabolic control, inflammation and gut microbiota in drug-naïve patients with type 2 diabetes: a pilot randomized trial. *Lipids Health Dis* 15:78
 114. Bibbins-Domingo K, Chertow GM, Coxson PG, Moran A, Lightwood JM, Pletcher MJ, Goldman L (2010) Projected effect of dietary salt reductions on future cardiovascular disease. *N Engl J Med* 362:590–599
 115. Wu GD, Chen J, Hoffmann C, Bittinger K, Chen YY, Keilbaugh SA, Bewtra M, Knights D, Walters WA, Knight R, Sinha R, Gilroy E, Gupta K, Baldassano R, Nessel L, Li H, Bushman FD, Lewis JD (2011) Linking long-term dietary patterns with gut microbial enterotypes. *Science* 334:105–108
 116. Silk DB, Davis A, Vulevic J, Tzortzis G, Gibson GR (2009) Clinical trial: the effects of a trans-galactooligosaccharide prebiotic on faecal microbiota and symptoms in irritable bowel syndrome. *Aliment Pharmacol Ther* 29:508–518
 117. Klinder A, Shen Q, Heppel S, Lovegrove JA, Rowland I, Tuohy KM (2016) Impact of increasing fruit and vegetables and flavonoid intake on the human gut microbiota. *Food Funct* 7:1788–1796
 118. Vaziri ND, Liu SM, Lau WL, Khazaeli M, Nazarteherani S, Farzaneh SH, Kieffer DA, Adams SH, Martin RJ (2014) High amylose resistant starch diet ameliorates oxidative stress, inflammation, and progression of chronic kidney disease. *PLoS ONE* 9:e114881
 119. Kieffer DA, Piccolo BD, Vaziri ND, Liu S, Lau WL, Khazaeli M, Nazarteherani S, Moore ME, Marco ML, Martin RJ, Adams SH (2016) Resistant starch alters gut microbiome and metabolomic profiles concurrent with amelioration of chronic kidney disease in rats. *Am J Physiol Renal Physiol* 310:F857–F871
 120. Richter CK, Skulas-Ray AC, Champagne CM, Kris-Etherton PM (2015) Plant protein and animal proteins: do they differentially affect cardiovascular disease risk? *Adv Nutr* 6:712–728
 121. Krishnamurthy VM, Wei G, Baird BC, Murtaugh M, Chonchol MB, Raphael KL, Greene T, Beddhu S (2012) High dietary fiber intake is associated with decreased inflammation and all-cause mortality in patients with chronic kidney disease. *Kidney Int* 81:300–306
 122. Pavan M (2016) Influence of prebiotic and probiotic supplementation on the progression of chronic kidney disease. *Minerva Urol Nefrol* 68:222–226
 123. Aliasgharzadeh A, Dehghan P, Gargari BP, Asghari-Jafarabadi M (2015) Resistant dextrin, as a prebiotic, improves insulin resistance and inflammation in women with type 2 diabetes: a randomised controlled clinical trial. *Br J Nutr* 113:321–330
 124. Torsdottir I, Alpsten M, Holm G, Sandberg AS, Tolli J (1991) A small dose of soluble alginate-fiber affects postprandial glycemia and gastric emptying in humans with diabetes. *J Nutr* 121:795–799
 125. Sola R, Godas G, Ribalta J, Vallve JC, Girona J, Anguera A, Ostos M, Recalde D, Salazar J, Caslake M, Martin-Lujan F, Salas-Salvado J, Masana L (2007) Effects of soluble fiber (*Plantago ovata* husk) on plasma lipids, lipoproteins, and apolipoproteins in men with ischemic heart disease. *Am J Clin Nutr* 85:1157–1163
 126. Eliasson K, Rytting KR, Hylander B, Rossner S (1992) A dietary fibre supplement in the treatment of mild hypertension. A randomized, double-blind, placebo-controlled trial. *J Hypertens* 10:195–199
 127. He J, Streiffer RH, Muntner P, Krousel-Wood MA, Whelton PK (2004) Effect of dietary fiber intake on blood pressure: a

- randomized, double-blind, placebo-controlled trial. *J Hypertens* 22:73–80
128. Zhu HL, Liu YL, Xie XL, Huang JJ, Hou YQ (2013) Effect of L-arginine on intestinal mucosal immune barrier function in weaned pigs after *Escherichia coli* LPS challenge. *Innate Immun* 19:242–252
 129. Tome-Carneiro J, Visioli F (2016) Polyphenol-based nutraceuticals for the prevention and treatment of cardiovascular disease: review of human evidence. *Phytomedicine* 23:1145–1174
 130. Hawrelak JA, Cattley T, Myers SP (2009) Essential oils in the treatment of intestinal dysbiosis: a preliminary in vitro study. *Altern Med Rev* 14:380–384
 131. Monda V, Villano I, Messina A, Valenzano A, Esposito T, Moscatelli F, Viggiano A, Cibelli G, Chieffi S, Monda M, Messina G (2017) Exercise modifies the gut microbiota with positive health effects. *Oxid Med Cell Longev* 2017:3831972
 132. Gobel RJ, Larsen N, Jakobsen M, Molgaard C, Michaelsen KF (2012) Probiotics to adolescents with obesity: effects on inflammation and metabolic syndrome. *J Pediatr Gastroenterol Nutr* 55:673–678
 133. Lamprecht M, Bogner S, Schippinger G, Steinbauer K, Fankhauser F, Hallstroem S, Schuetz B, Greilberger JF (2012) Probiotic supplementation affects markers of intestinal barrier, oxidation, and inflammation in trained men; a randomized, double-blinded, placebo-controlled trial. *J Int Soc Sports Nutr* 9:45
 134. Miranda Alatríste PV, Urbina Arronte R, Gomez Espinosa CO, Espinosa Cuevas MDLA (2014) Effect of probiotics on human blood urea levels in patients with chronic renal failure. *Nutr Hosp* 29:582–590
 135. Ranganathan N, Ranganathan P, Friedman EA, Joseph A, Delano B, Goldfarb DS, Tam P, Rao AV, Anteyi E, Musso CG (2010) Pilot study of probiotic dietary supplementation for promoting healthy kidney function in patients with chronic kidney disease. *Adv Ther* 27:634–647
 136. Abbasi B, Ghiasvand R, Mirlohi M (2017) Kidney function improvement by soy milk containing *Lactobacillus plantarum* A7 in type 2 diabetic patients with nephropathy: a double-blinded randomized controlled trial. *Iran J Kidney Dis* 11:36–43
 137. Khalesi S, Sun J, Buys N, Jayasinghe R (2014) Effect of probiotics on blood pressure: a systematic review and meta-analysis of randomized, controlled trials. *Hypertension* 64:897–903
 138. Yacoub R, Kaji D, Patel SN, Simoes PK, Busayavalasa D, Nadkarni GN, He JC, Coca SG, Uribarri J (2016) Association between probiotic and yogurt consumption and kidney disease: insights from NHANES. *Nutr J* 15:10
 139. Uusitalo U, Liu X, Yang J, Aronsson CA, Hummel S, Butterworth M, Lernmark Å, Rewers M, Hagopian W, She J-X, Simell O, Toppari J, Ziegler AG, Akolkar B, Krischer J, Norris JM, Virtanen SM (2016) Association of early exposure of probiotics and islet autoimmunity in the TEDDY Study. *JAMA Pediatr* 170:20–28
 140. Kasinska MA, Drzewoski J (2015) Effectiveness of probiotics in type 2 diabetes: a meta-analysis. *Pol Arch Med Wewn* 125:803–813
 141. Brugere JF, Borrel G, Gaci N, Tottey W, O'Toole PW, Malpuech-Brugere C (2014) Archaeobiotics: proposed therapeutic use of archaea to prevent trimethylaminuria and cardiovascular disease. *Gut Microbes* 5:5–10
 142. Prakash S, Chang TM (1996) Microencapsulated genetically engineered live *E. coli* DH5 cells administered orally to maintain normal plasma urea level in uremic rats. *Nat Med* 2:883–887
 143. Zhao S, Liu W, Wang J, Shi J, Sun Y, Wang W, Ning G, Liu R, Hong J (2017) *Akkermansia muciniphila* improves metabolic profiles by reducing inflammation in chow diet-fed mice. *J Mol Endocrinol* 58:1–14
 144. Zeng YQ, Dai Z, Lu F, Lu Z, Liu X, Chen C, Qu P, Li D, Hua Z, Qu Y, Zou C (2016) Emodin via colonic irrigation modulates gut microbiota and reduces uremic toxins in rats with chronic kidney disease. *Oncotarget* 7:17468–17478
 145. Napolitano A, Miller S, Nicholls AW, Baker D, Van Horn S, Thomas E, Rajpal D, Spivak A, Brown JR, Nunez DJ (2014) Novel gut-based pharmacology of metformin in patients with type 2 diabetes mellitus. *PLoS ONE* 9:e100778
 146. Mishima E, Fukuda S, Shima H, Hirayama A, Akiyama Y, Takeuchi Y, Fukuda NN, Suzuki T, Suzuki C, Yuri A, Kikuchi K, Tomioka Y, Ito S, Soga T, Abe T (2015) Alteration of the intestinal environment by lubiprostone is associated with amelioration of adenine-induced CKD. *J Am Soc Nephrol* 26:1787–1794
 147. Niwa T, Nomura T, Sugiyama S, Miyazaki T, Tsukushi S, Tsutsui S (1997) The protein metabolite hypothesis, a model for the progression of renal failure: an oral adsorbent lowers indoxyl sulfate levels in undialyzed uremic patients. *Kidney Int Suppl* 62:S23–S28
 148. Navarro-Gonzalez JF, Mora-Fernandez C, Muros de Fuentes M, Donate-Correa J, Cazana-Perez V, Garcia-Perez J (2011) Effect of phosphate binders on serum inflammatory profile, soluble CD14, and endotoxin levels in hemodialysis patients. *Clin J Am Soc Nephrol* 6:2272–2279
 149. Ellis RJ, Small DM, Vesey DA, Johnson DW, Francis R, Vitetta L, Gobe GC, Morais C (2016) Indoxyl sulphate and kidney disease: causes, consequences and interventions. *Nephrology (Carlton)* 21:170–177
 150. Nallu A, Sharma S, Ramezani A, Muralidharan J, Raj D (2017) Gut microbiome in chronic kidney disease: challenges and opportunities. *Transl Res* 179:24–37