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Authors
Sumida, Keiichi
Lau, Wei Ling
Kovesdy, Csaba P
et al.

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Microbiome modulation as a novel therapeutic approach in chronic kidney disease

Keiichi Sumida[a], *Wei Ling Lau*[b], *Csaba P. Kovesdy*[a,c], *Kamyar Kalantar-Zadeh*[b], *and Kourosh Kalantar-Zadeh*[d]

Purpose of review
Gut dysbiosis has been implicated in the pathogenesis of chronic kidney disease (CKD). Interventions aimed at restoring gut microbiota have emerged as a potential therapeutic option in CKD. This review summarizes the current evidence on gut microbiota-targeted strategies in patients with CKD.

Recent findings
A growing number of studies have shown that plant-based diets, low-protein diets, prebiotic, probiotic, and synbiotic supplementation, and constipation treatment may lead to favorable alterations in the gut microbiota. Current evidence suggests that the implementation of both plant-based and low-protein diets has potential benefits for the primary prevention of CKD, and for slowing CKD progression, with minimal risk of hyperkalemia and/or cachexia. The use of prebiotics, probiotics, and synbiotics and laxatives may have beneficial effects on uremic toxin generation, but their evidence is limited for the prevention and treatment of CKD. Recent advances in diagnostic technologies (e.g., high-throughput sequencing and nanotechnology) could enhance rapid diagnosis, monitoring, and design of effective therapeutic strategies for mitigating gut dysbiosis in CKD.

Summary
Plant-based and low-protein diets, prebiotic, probiotic, and synbiotic supplementation, and constipation treatment represent novel gut microbiota-targeted strategies in the conservative management of CKD, which could improve clinical outcomes in CKD.

Keywords
chronic kidney disease, constipation, microbiome, nanotechnology, plant-based diet

INTRODUCTION

The recent explosion of scientific interest in the gut microbiota has dramatically advanced our understanding of its complex pathophysiologic interactions with multiple organs in health and disease. Emerging evidence has revealed that the gut microbiota is significantly altered in patients with chronic kidney disease (CKD) [1], contributing to the pathogenesis of progression of CKD and its complications [e.g., cardiovascular disease (CVD)], often referred to as the 'gut–kidney' or 'gut–kidney–heart' axes [2,3]. Uncovering these multidirectional interactions have in turn led to a growing interest in the clinical utility of gut microbiota-targeted interventions for the prevention and treatment of CKD [4]. Herein, we provide a narrative review of potential therapeutic strategies targeting gut microbiota modulation in CKD.

SYMBIOTIC INTERACTIONS BETWEEN HOST AND GUT MICROBIOTA

For millions of years, the gut microbiota has coevolved with the human host and their symbiotic interactions provide the host with various benefits [1]. The human gastrointestinal tract harbors more than 100 trillion individual microbes including

[a]Division of Nephrology, Department of Medicine, University of Tennessee Health Science Center, Memphis, Tennessee, [b]Division of Nephrology and Hypertension, Department of Medicine, University of California Irvine, Orange, California, [c]Nephrology Section, Memphis VA Medical Center, Memphis, Tennessee, USA and [d]School of Chemical Engineering, University of New South Wales, Kensington, New South Wales, Australia

Correspondence to Kourosh Kalantar-Zadeh, PhD, School of Chemical Engineering, University of New South Wales, Kensington 2052, NSW, Australia. Tel: +61 2 938 54126; e-mail: k.kalantar-zadeh@unsw.edu.au

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KEY POINTS

- Plant-based diets, low-protein diets, prebiotic, probiotic, and synbiotic supplementation, and constipation treatment can shift the gut microbiota profile towards reduced production of uremic toxins.
- Both plant-based and low-protein diets have potential benefits for primary prevention of CKD, as well as for slowing CKD progression, with minimal risk of hyperkalemia and/or cachexia.
- Currently, limited evidence supports the use of prebiotics, probiotics, and synbiotics and laxatives in the prevention and treatment of CKD.
- New technologies could contribute to rapid diagnosis, monitoring, and design of effective therapeutic strategies targeting gut microbiota in CKD.

2000–4000 species [5–7]. The commensal or symbiotic gut microbiota contains three major domains of microorganisms including bacteria, archaea, and eukarya [7], encoding at least 150-fold more genes than the human genome [8]. In healthy individuals, the gut microbiota is generally dominated by two anaerobic bacterial phyla, Firmicutes and Bacteroidetes, out of over 50 bacterial phyla that also include Actinobacteria, Proteobacteria, Cyanobacteria, and Fusobacteria [9,10].

Under physiologic conditions, the gut microbiota participates in a variety of metabolic activities and thus can be considered as a metabolically active endogenous organ in itself [4]. These complementary metabolic activities include production of short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate [11], synthesis of certain vitamins (e.g., vitamin K6 and vitamin B group) [12], degradation of undigestible plant polysaccharides and oxalates [13], and biotransformation of conjugated bile acids [14]. In addition, the gut microbiota protects against pathogens by inhibiting their colonization via the production of antibiotics and bacteriocins [15,16], and is also involved in the development, maturation, and maintenance of gastrointestinal motility and in shaping the mucosal immune system and intestinal barrier [16,17]. Changes in the composition and function of the gut microbiota, have been associated with a variety of medical problems and illnesses including obesity [18], hypertension [19], cancers [20], CVD [21], and CKD [2].

GUT DYSBIOSIS IN CHRONIC KIDNEY DISEASE

Emerging evidence has revealed that patients with CKD show significant alterations of the gut microbiota (a.k.a. gut dysbiosis) in specific microbial taxa of both aerobic and anaerobic bacteria [22]. In a study comparing the composition of the gut microbiota between CKD and control rats, Vaziri *et al.* [1] demonstrated a significant difference in the abundance of 175 bacterial operational taxonomic units (OTUs), which are microbial genomic sequences clustered by sequence similarity, with a notable decrease in Lactobacillaceae and Prevotellaceae families in the CKD animals. Further, they showed a significant difference in the abundance of 190 bacterial OTUs between patients with end-stage renal disease (ESRD) and healthy individuals [1]. Other groups have reported that the number of Enterobacteriaceae (especially Enterobacter, Klebsiella, and Escherichia), Enterococci and Clostridium perfringens were significantly higher in patients with ESRD than in healthy controls [23,24].

One of the contributing factors to the gut dysbiosis in CKD is changes in the biochemical environment due to accumulation of retained metabolic waste products (such as urea) which diffuse into the gut. Bacterial urease of the gut microbiota hydrolyzes urea and produces large quantities of ammonia and ammonium hydroxide, which raises luminal pH and alters gut microbial subpopulations [15,25]. Restricted intake of high-fiber products to avoid hyperkalemia [26] also impacts the gut microbiota. The CKD milieu combined with low-fiber diet shifts the microbiome from a saccharolytic (carbohydrate-fermenting) to a more proteolytic phenotype which generates gut-derived uremic toxins from amino acid catabolism [e.g., indoxyl sulfate, p-cresyl sulfate and trimethylamine-*N*-oxide (TMAO)] [27]. Other pathways that contribute to gut dysbiosis in CKD include medication use (e.g., phosphate binders, iron, and antibiotics) [28–30], metabolic acidosis [31], and slow intestinal transit time [32]. It is important to note that all of these factors have been suggested to account for the intestinal barrier dysfunction in patients with CKD [33–35], allowing translocation of gut-derived products, such as gut-derived uremic toxins (e.g., indoxyl sulfate, TMAO, etc.), bacterial endotoxins (i.e., lipopolysaccharide) and DNA fragments, and intact bacteria, into the systemic circulation. The translocation of these gut-derived products can contribute to the activation of host inflammatory responses, which have been associated with excess morbidity and mortality in patients with CKD [17,36–38] (Figs. 1 and 2).

STRATEGIES TARGETING GUT DYSBIOSIS IN CHRONIC KIDNEY DISEASE

Improved understanding of the pathologic roles of gut dysbiosis has triggered enormous interest and

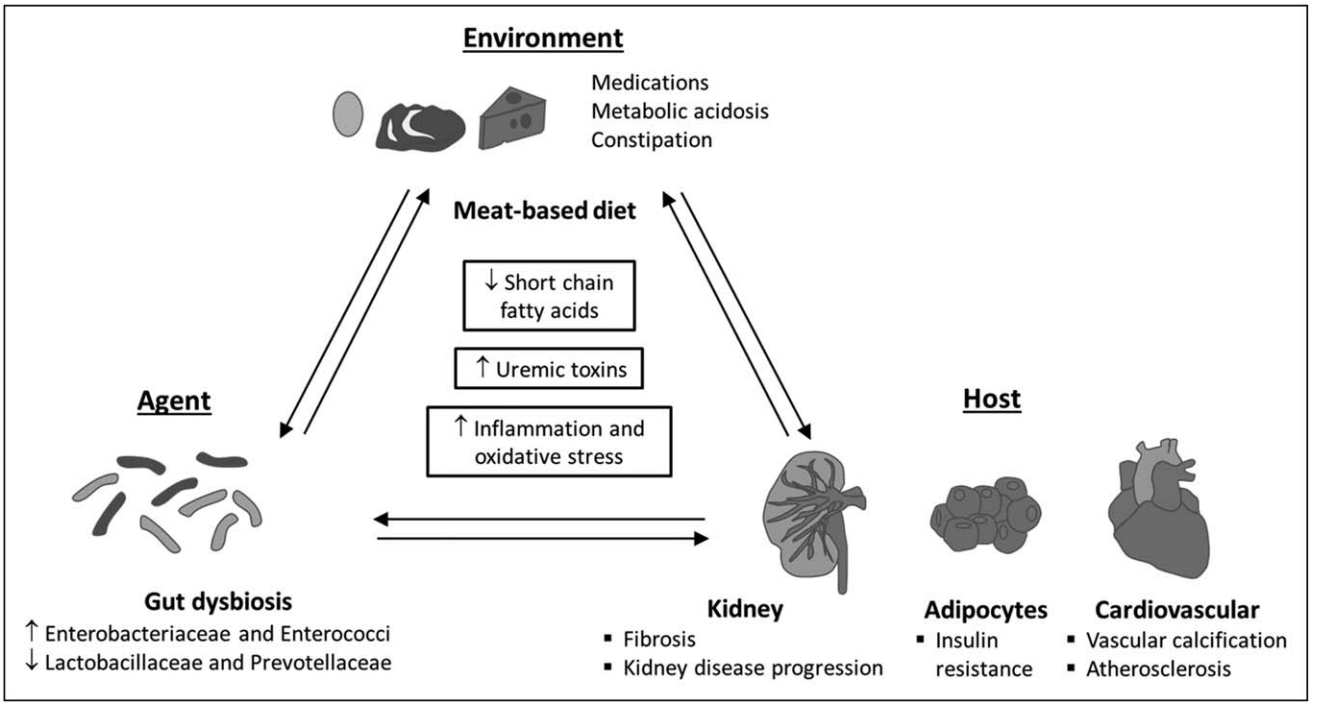

FIGURE 1. Interaction between environment, agent, and host in chronic kidney disease.

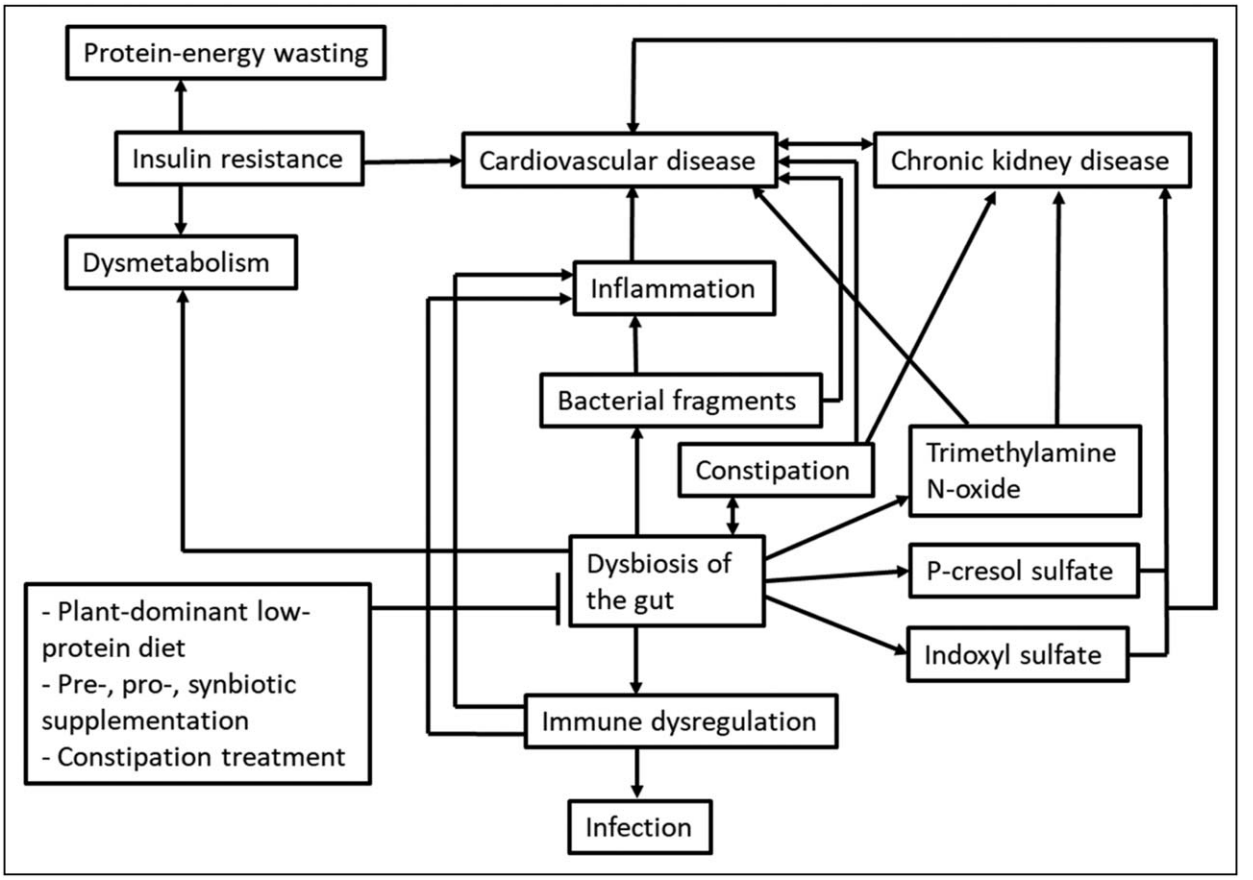

FIGURE 2. Potential pathways linking gut dysbiosis to protein-energy wasting, cardiovascular disease, and chronic kidney disease.

Table 1. Potential clinical benefits from gut microbiota-targeted strategies in chronic kidney disease

Therapeutic strategies	Potential benefits
Plant-based diet	Reductions in inflammatory markers blood urea nitrogen uremic toxins proteinuria Improved controls of metabolic acidosis lipid metabolism mineral bone disorders body weight blood pressure bowel habits Slowing CKD progression
Low-protein diet	Reductions in inflammatory markers blood urea nitrogen uremic toxins proteinuria Improved controls of metabolic acidosis mineral bone disorders blood pressure Slowing CKD progression Improvement of physical function
Probiotic, prebiotic, and synbiotic supplements	Reductions in inflammatory markers blood urea nitrogen uremic toxins Normalization of bowel habits
Constipation treatment	Reduction in uremic toxin X Improvement of gut motility Lowering incidence of hyperkalemia Slowing CKD progression

CKD, chronic kidney disease.

vigorous efforts to the development of several therapeutic strategies aimed at re-establishing symbiotic status of the gut microbiota [4]. These include dietary modifications [e.g., plant-based diet and low-protein diet (LPD)] [39▪▪,40,41], dietary supplementation of prebiotics (i.e., nondigestible food ingredients that induce specific modifications in the composition and/or activity of the gut microbiota) [42], probiotics (i.e., live microorganisms which confer health beneficial effects when administered in adequate amounts to the host) [43], and synbiotics (i.e., both probiotics and prebiotics) [44], and constipation treatment [45▪] (Table 1).

Plant-based diet

Plant-based diets have been used with growing popularity for the treatment of a wide range of lifestyle-related diseases, including diabetes, hypertension, obesity, and CKD [46▪]. This dietary pattern focuses primarily on plant products, such as whole grains, seeds, nuts, legumes, fruits, vegetables, tubers and starchy vegetables, while minimizing animal products including meat, fish, eggs and dairy [41] (Fig. 3).

Dietary fibers are one of the important sources for intestinal bacterial fermentation [47], and hence have been extensively studied with the aim of modulating gut microbiota [48,49]. Dietary fibers of edible plants comprise of insoluble and soluble carbohydrates (e.g., cellulose, lignin, and nonstarch polysaccharides) and nondigestible oligosaccharides and resistant starch [50]. The nondigestible fiber components pass intact into the large intestine, increase viscosity and bulking of the fecal matter [51], and more importantly undergo fermentation by the resident anaerobic microbiota (mainly by Bacteroidetes and Firmicutes) into intestinal gases and SCFAs that play a vital role in regulating the homeostasis of human body and progression of diseases [11,52,53▪]. Specifically, SCFAs serve as important energy resources for colonic epithelial cells and maintain the integrity of the epithelial barrier function by regulating tight junction proteins such as occluding, claudin-1, and Zonula Occludens-1 [54,55]. In addition, SCFAs enhance the modulation of host immune responses and thereby protect the intestinal epithelium [56–58]. In fact, consumption of diet enriched with amylose resistant starch, a fermentable and indigestible complex carbohydrates, have been shown to improve gut microbial dysbiosis, attenuate inflammation and oxidative stress, ameliorate metabolic disorders, and retard progression of kidney disease in CKD rats [59,60].

Other than dietary fibers, fractions of unabsorbed dietary fat reach the large intestine and thus can potentially be substrates that differentially influence the microbial system [61,62]. While Western diets rich in saturated fats and low in antioxidants, phytosterols, and other phytochemicals have been shown to change gut microbiota favoring a proinflammatory state [63], linoleic acid, mainly coming from plant sources, are utilized by different gut microbial species to produce conjugated linoleic acid that has shown anti-inflammatory, antiadipogenic, antidiabetogenic, and anticarcinogenic properties [64]. Another common benefit of plant-based diets is that they could lead to less production of uremic toxins and reduced glomerular hyperfiltration associated with excess protein intake [46▪].

From an epidemiological perspective, the beneficial effects of a plant-based diet in CKD have been reported in several observational studies and clinical trials [65–70]. In an observational study of 15 vegetarians and 11 individuals consuming an unrestricted diet, the production rates of p-cresol

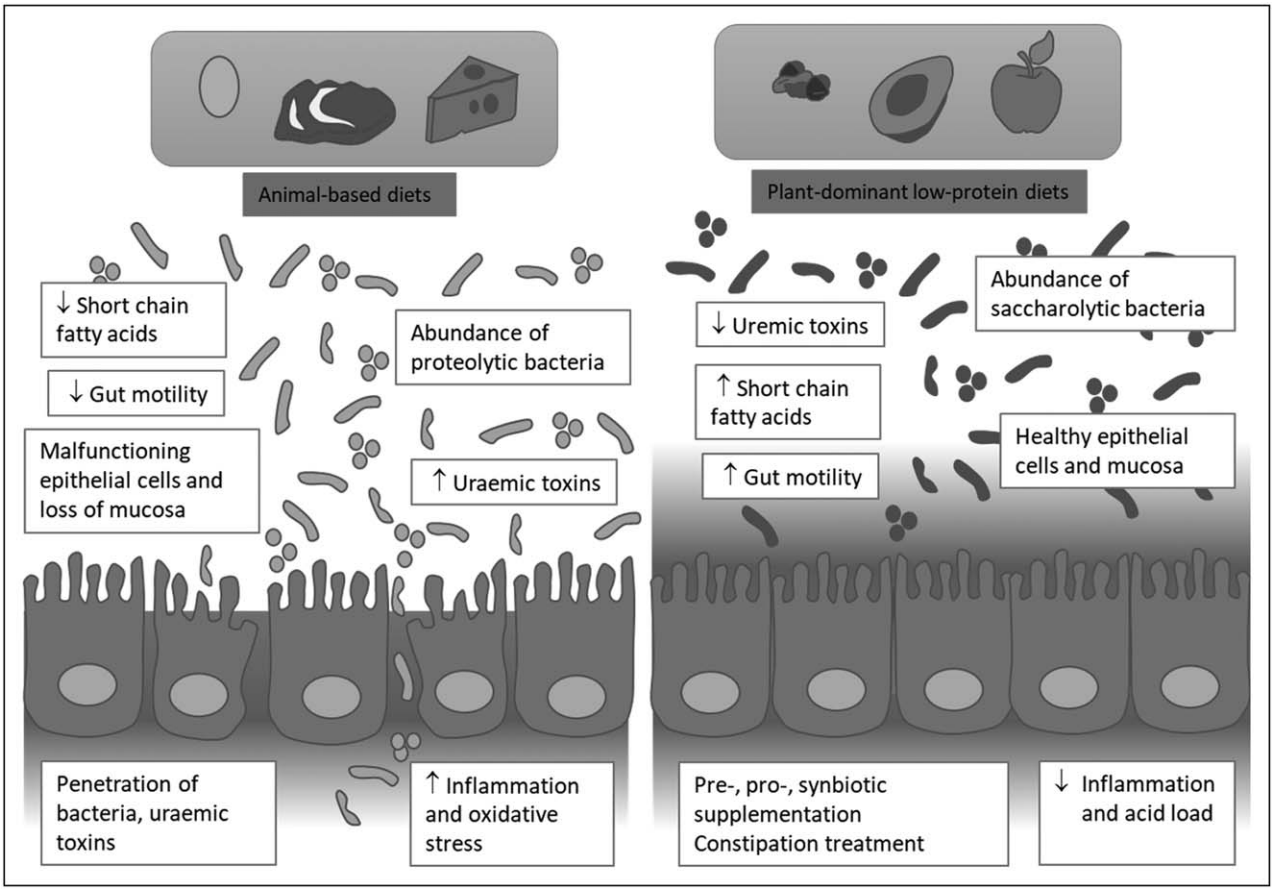

FIGURE 3. The effects of animal-based and plant-dominant low-protein diets on the gut microbiota and uremic milieu in chronic kidney disease.

sulfate and indoxyl sulfate were markedly lower in vegetarians than in individuals consuming an unrestricted diet [71]. Using a prospective cohort of 14 686 middle-aged adults in the Atherosclerosis Risk in Communities study, Kim *et al.* [67] showed that higher (vs. lower) adherence to a plant-based diet was significantly associated with lower risk of incident CKD and slower estimated glomerular filtration rate decline. In the three seminal trials examining the effects of fruits and vegetables (vs. oral bicarbonate) on metabolic acidosis and kidney outcomes, Goraya *et al.* demonstrated a favorable effect of these diets on the treatment of metabolic acidosis in CKD, even in its advanced stages, with additional benefits of reducing urine albumin-to-creatinine ratio, weight, and SBP [72–74]. Moreover, plant-based foods have a lower phosphorus content than other food sources, and plant phosphorus which binds to phytate has a lower bioavailability than animal phosphorus [75,76]. In fact, plant-based (vs. meat-based) diets have been associated with lower levels of serum phosphorus and fibroblast growth factor-23 in CKD patients [77]. It is important to note that the concern of hyperkalemia related to a plant-based diet has not been supported by current scientific evidence [46▪], presumably due to the enhancement of bowel motility and alkalization induced by plant-based dietary sources [78–81].

Low-protein diet

Low-protein diet, defined as dietary protein intake 0.6–0.8 g/kg/day, has long been considered as an option of conservative management for patients with nondialysis-dependent CKD (NDD-CKD) who wish to avoid or defer dialysis initiation and to retard the progression of CKD [82,83]. While several mechanisms have been suggested for the potential renoprotective benefits of LPD, including lower intraglomerular pressure, alleviation of metabolic acidosis, and lower phosphorus burden [83], the major benefits of LPD potentially attributable to gut microbiota modulation may be through reduced production of uremic toxins, such as p-cresyl sulfate, indoxyl sulfate, and TMAO [27]. p-Cresyl sulfate, for example, is a 188-Da protein-bound solute that originates from sulfation of the intestinally generated p-cresol, which is a colonic fermentation

product of the amino acid tyrosine and phenylalanine via deaminase enzymes produced by Bacteroides, Bifidobacterium, Lactobacillus, Enterobacter, and Clostridium genera [84,85]. Indoxyl sulfate, on the other hand, is a protein-bound uremic toxin generated from bacterial tryptophanase, which is expressed by Clostridiaceae, Enterobacteriaceae, and Verrucomicrobiaceae [27,84]. TMAO is a circulating organic compound derived from bacterial metabolism of dietary L-carnitine and choline [86,87]. Importantly, all of these gut-derived uremic toxins have been associated with higher risk of CKD progression, CVD, and mortality [88–91], suggesting that the modulation of gut microbiota towards reduced production of uremic toxins could be a novel therapeutic option for adverse outcomes in CKD.

There are a few studies that support utilizing LPDs as possible gut microbiota-targeted interventions. In an observational study of 30 NDD-CKD patients undergoing LPD for 6 months, Black *et al.* [92] demonstrated that those who adhere (vs. did not adhere) to the LPD had significantly lower levels of serum p-cresyl sulfate, along with the change in the gut microbiome profile. Similarly, a recent pre-post study of 16 CKD patients found that a 6-month intervention with a LPD significantly modified gut microbiota and modulated inflammatory and metabolic parameters [93▪]. The study also showed a significant improvement of physical function scores after the LPD intervention [93▪]. Other beneficial effects, such as higher serum bicarbonate levels, lower phosphorus levels, lower azotemia, and lower risk of CKD progression associated with the intervention with LPDs, have also been reported in several clinical trials [82].

Since a plant (vs. animal) protein intake has been associated with lower risk of incident CKD [66], the source of protein, as well as its amount, may need to be considered for the implementation of a LPD in patients with CKD. In this context, a plant-dominant LPD (a.k.a. PLADO, defined as a type of LPD with dietary protein intake of 0.6–0.8 g/kg/day with at least 50% plant-based sources) recently proposed by Kalantar-Zadeh *et al.* [39▪▪] may be of high biologic value (Fig. 3). In addition, given that coronavirus disease 2019 (COVID-19) susceptibility and severity may be related to gut microbiome [94] and since COVID-19 can cause acute kidney injury including through direct kidney involvement [95] modulating microbiome including by PLADO may have additional favorable impact on both infection control and kidney health. Future studies should examine the effects of PLADO regimens on gut microbiota and on clinical outcomes in CKD.

Supplementation of prebiotics, probiotics, and synbiotics

Prebiotics, probiotics, and synbiotics have become familiar to the public as the components of dietary supplements and bioyogurt, and the administration of these supplements is increasingly recognized as a potential gut microbiota-targeted intervention for CKD patients. In a recent systematic review and meta-analysis of 16 randomized controlled trials investigating the effects of prebiotics, probiotics, and/or synbiotic supplementation (>1 week) in patients with CKD, McFarlane *et al.* [96] reported that the synbiotic supplementation led to higher abundances of Bifidobacterium and Lachnospiraceae and a decrease in Ruminococcaceae, and that prebiotic supplementation led to a slight but significant reduction in serum urea concentration. Although a few trials demonstrated a favorable change in serum p-cresyl sulfate [97,98], there was a low certainty of evidence to support the overall treatment effect of prebiotic, probiotic, and synbiotic supplementation on uremic toxins, as well as on serum creatinine, blood glucose, total cholesterol, low-density cholesterol, high-density cholesterol, triglyceride, and weight [96]. Currently, there is insufficient evidence to conclude whether one type of nutrition supplementation is superior to another. Future well designed clinical trials are needed to establish the appropriate microbiota-targeted supplementation formulation and to confirm its effectiveness on patient-centered clinical outcomes.

Constipation treatment

Constipation is one of the most common gastrointestinal disorders among patients with CKD, due in part to low fiber and fluid intake, concomitant medications, and multiple comorbidities. Although constipation is usually perceived as a benign condition, recent epidemiological studies have revealed its independent associations with adverse clinical outcomes such as ESRD, CVD, and mortality [99,100]. The adequate management of constipation may therefore be more important than previously considered, and gut microbiota-targeted interventions would be a reasonable option for constipation management in CKD [45▪].

The alterations of gut microbiota in patients with constipation has been characterized by a relative decrease in obligate anaerobic bacteria (e.g., Bifidobacterium and Lactobacillus genus) and a parallel increase in potentially pathogenic microorganisms (e.g., Enterobacteriaceae family) [101–103]. A recent study reported that the overall microbial composition of the colonic mucosa was associated with constipation, and constipated patients (in comparison

with healthy controls) had a significantly higher abundance of phylum Bacteroidetes in the colon [104]. These alterations of microbiota have been suggested to influence gastrointestinal motility through several mechanisms, such as the release of bacterial end-products, intestinal neuroendocrine factors, and mediators in the gut immune response [105]. For example, the decrease in relative abundance of anaerobic bacteria could result in reduced production of SCFAs that stimulate ileal and colonic smooth muscle contractility and could thereby contribute to constipation [101]. The increase in relative abundance of methanogenic microbes such as archaeae can also cause constipation through increased methane production that reduces gut motility [106].

Nonpharmacological treatment is traditionally considered the first step of a comprehensive management of constipation [107–110]. Although patients with CKD are typically advised to restrict the intake of fiber-rich foods to prevent hyperkalemia, given the lack of evidence supporting this concern and the scientific premise of a plant-based diet (vide supra), the potential health and gastrointestinal benefits of dietary fiber, along with its low cost, may justify consideration of a plant-based, fiber-rich diet as a first step in the management of constipation in CKD. This is also supported by the fact that the gut plays an increasing role in intestinal potassium wasting in CKD and constipation is a likely contributor to hyperkalemia in CKD [45▪]. Pharmacological interventions may often be required for secondary (e.g., drug-induced) constipation, which is predominant in CKD patients and is unlikely to respond well to nonpharmacological treatment alone. In fact, the use of laxatives has been shown to increase considerably as patients progressed to ESRD [111]. Among a wide range of pharmacological treatments currently available, a few types of laxative agents, such as lactulose, a chloride channel activator (lubiprostone), and a guanylate cyclase C agonist (linaclotide), have been shown to have unique pharmacological properties for gut microbiota modulation, along with a reduction in circulating levels of uremic toxins [112–115]. Although the issues of high drug costs and long-term safety profiles remain to be addressed, given the close links of gut dysbiosis with both CKD and constipation, the gut microbiota-targeted approach using these drugs seems particularly relevant to the constipation management in patients with CKD.

DEVELOPMENT OF MICROBIOME DIAGNOSTICS

Analyzing the composition of the human gut microbiota has long been dependent on culturing methods, which access only a tiny subset of the broad diversity of microorganisms [116]. With the recent advances of innovative analytical technologies, culture-independent molecular identification of species in the gut microbiota has become the main diagnostics. Among various high-throughput methods, next-generation sequencing technologies have revolutionized our view of microbial communities [117]. The DNA sequencing methodology has allowed us to characterize and analyze microbiomes with greater accuracy and precision and with less bias, compared with culture-based approaches [117]. A common approach used to identify bacterial populations is based on sequencing of the bacterial 16S ribosomal RNA (rRNA) subunit [117]. Hypervariable regions within this gene contain species-specific sequences, which allow identification of the bacteria of origin by comparing with reference databases [118]. Based on the sequences of the internal transcribed spacer region lying between the fungal 18S and 5.8S rRNA genes, fungal populations can also be identified [119]. Increasing throughput and decreasing costs associated with gene sequencing, along with the development of computational tools for resultant sequence data analyses, have made these approaches more feasible to identify and characterize microbial communities in various disease states including CKD [117].

Another emerging and future frontier to influence the gut microbiota manipulation and hence CKD management is nanotechnology. Nanotechnology, or systems/device manufacture at the molecular level, is a multidisciplinary scientific field undergoing explosive development and substantially contributing to molecular diagnostics in current medicine [120]. Recent progress in nanotechnology has been directed toward understanding the microbiomes of humans, as well as animals, plants, and even the ocean and the atmosphere [121]. The great advantage of nanotechnology in studying microbiomes is that the nanoscale is the scale of function in biology, and the application of this technology enables microbial community manipulation, chemical analysis, and imaging [122], potentially leading to rapid diagnosis, monitoring, and design of effective therapeutic actions for conditions linked to gut dysbiosis, such as CKD. For example, noninvasive breath tests, with arrays of nanomaterials, can identify the presence of volatile organic compounds with the signatures of modulated microbiota (e.g., abundance of Prevotella) and hence could lead to quick diagnosis and monitoring of certain conditions in CKD [53▪,122,123]. Ingestible sensors could be designed for the detection of a specific type of uremic toxins derived from gut microbiota [124]. Nanotechnology could also

efficiently be implemented in designing intelligent drugs or functional foods, with the possibility of localized delivery in the gut [125–127]. Although still at an early stage, there are a few precision antimicrobials that have shown efficacy in model systems of human disease [128,129]. These precision antimicrobials, as well as genetically engineered bacteria, could help restore symbiotic bacterial populations in the gut and reduce levels of gut-derived uremic toxins in patients with CKD [122,130].

CONCLUSION

The gut microbiota is significantly altered in patients with CKD, leading to structural and functional disruption of the intestine and intestinal epithelial barrier. The reduced gastrointestinal motility and increased gut permeability allows translocation of gut-derived uremic toxins and bacterial fragments into the systemic circulation and contributes to adverse clinical outcomes in CKD through activation of inflammatory responses. Strategies aimed at restoring gut microbiota composition are a novel therapeutic option. Although evidence from clinical trials is currently limited, interventions such as plant-based diet, LPD, prebiotic, probiotic, and synbiotic supplementation, and constipation treatment have shown some benefit in terms of attenuating gut microbial alterations and reducing circulating levels of uremic toxins. With the use of emerging technologies, more in-depth clinical trials should examine the impact of gut microbiota-targeted interventions on clinical outcomes in CKD.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Vaziri ND, Wong J, Pahl M, *et al.* Chronic kidney disease alters intestinal microbial flora. Kidney Int 2013; 83:308–315.
2. Pahl MV, Vaziri ND. The chronic kidney disease – colonic axis. Semin Dial 2015; 28:459–463.
3. Sumida K, Kovesdy CP. The gut–kidney–heart axis in chronic kidney disease. Physiol Int 2019; 106:195–206.
4. Ramezani A, Massy ZA, Meijers B, *et al.* Role of the gut microbiome in uremia: a potential therapeutic target. Am J Kidney Dis 2016; 67:483–498.
5. Whitman WB, Coleman DC, Wiebe WJ. Prokaryotes: the unseen majority. Proc Natl Acad Sci U S A 1998; 95:6578–6583.
6. Malnick S, Melzer E. Human microbiome: from the bathroom to the bedside. World J Gastrointest Pathophysiol 2015; 6:79–85.
7. Siezen RJ, Kleerebezem M. The human gut microbiome: are we our enterotypes? Microb Biotechnol 2011; 4:550–553.
8. Turnbaugh PJ, Ley RE, Hamady M, *et al.* The human microbiome project. Nature 2007; 449:804–810.
9. Eckburg PB, Bik EM, Bernstein CN, *et al.* Diversity of the human intestinal microbial flora. Science 2005; 308:1635–1638.
10. Tremaroli V, Backhed F. Functional interactions between the gut microbiota and host metabolism. Nature 2012; 489:242–249.
11. Levy M, Thaiss CA, Elinav E. Metabolites: messengers between the microbiota and the immune system. Genes Dev 2016; 30:1589–1597.
12. Hill MJ. Intestinal flora and endogenous vitamin synthesis. Eur J Cancer Prev 1997; 6(Suppl 1):S43–S45.
13. Hooper LV, Midtvedt T, Gordon JI. How host–microbial interactions shape the nutrient environment of the mammalian intestine. Annu Rev Nutr 2002; 22:283–307.
14. Hylemon PB, Harder J. Biotransformation of monoterpenes, bile acids, and other isoprenoids in anaerobic ecosystems. FEMS Microbiol Rev 1998; 22:475–488.
15. Wong J, Piceno YM, DeSantis TZ, *et al.* 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 2014; 39:230–237.
16. Gerritsen J, Smidt H, Rijkers GT, *et al.* Intestinal microbiota in human health and disease: the impact of probiotics. Genes Nutr 2011; 6:209–240.
17. Vaziri ND, Zhao YY, Pahl MV. Altered intestinal microbial flora and impaired epithelial barrier structure and function in CKD: the nature, mechanisms, consequences and potential treatment. Nephrol Dial Transplant 2016; 31:737–746.
18. Kang Y, Cai Y. Gut microbiota and obesity: implications for fecal microbiota transplantation therapy. Hormones (Athens) 2017; 16:223–234.
19. Adnan S, Nelson JW, Ajami NJ, *et al.* Alterations in the gut microbiota can elicit hypertension in rats. Physiol Genomics 2017; 49:96–104.
20. Raskov H, Burcharth J, Pommergaard HC. Linking gut microbiota to colorectal cancer. J Cancer 2017; 8:3378–3395.
21. Carding S, Verbeke K, Vipond DT, *et al.* Dysbiosis of the gut microbiota in disease. Microb Ecol Health Dis 2015; 26:26191.
22. Simenhoff ML, Dunn SR, Zollner GP, *et al.* Biomodulation of the toxic and nutritional effects of small bowel bacterial overgrowth in end-stage kidney disease using freeze-dried Lactobacillus acidophilus. Miner Electrolyte Metab 1996; 22:92–96.
23. Hida M, Aiba Y, Sawamura S, *et al.* Inhibition of the accumulation of uremic toxins in the blood and their precursors in the feces after oral administration of Lebenin, a lactic acid bacteria preparation, to uremic patients undergoing hemodialysis. Nephron 1996; 74:349–355.
24. Wang F, Jiang H, Shi K, *et al.* Gut bacterial translocation is associated with microinflammation in end-stage renal disease patients. Nephrology (Carlton) 2012; 17:733–738.
25. Vaziri ND. CKD impairs barrier function and alters microbial flora of the intestine: a major link to inflammation and uremic toxicity. Curr Opin Nephrol Hypertens 2012; 21:587–592.
26. Kalantar-Zadeh K, Kopple JD, Deepak S, *et al.* Food intake characteristics of hemodialysis patients as obtained by food frequency questionnaire. J Ren Nutr 2002; 12:17–31.
27. Lau WL, Savoj J, Nakata MB, *et al.* Altered microbiome in chronic kidney disease: systemic effects of gut-derived uremic toxins. Clin Sci (Lond) 2018; 132:509–522.
28. Kortman GAM, Reijnders D, Swinkels DW. Oral iron supplementation: potential implications for the gut microbiome and metabolome in patients with CKD. Hemodial Int 2017; 21(Suppl 1):S28–S36.
29. Lau WL, Vaziri ND, Nunes ACF, *et al.* The phosphate binder ferric citrate alters the gut microbiome in rats with chronic kidney disease. J Pharmacol Exp Ther 2018; 367:452–460.
30. Vangay P, Ward T, Gerber JS, *et al.* Antibiotics, pediatric dysbiosis, and disease. Cell Host Microbe 2015; 17:553–564.

31. Goraya N, Wesson DE. Acid-base status and progression of chronic kidney disease. Curr Opin Nephrol Hypertens 2012; 21:552–556.
32. Wu MJ, Chang CS, Cheng CH, *et al.* Colonic transit time in long-term dialysis patients. Am J Kidney Dis 2004; 44:322–327.
33. Andersen K, Kesper MS, Marschner JA, *et al.* Intestinal dysbiosis, barrier dysfunction, and bacterial translocation account for CKD-related systemic inflammation. J Am Soc Nephrol 2017; 28:76–83.
34. Meijers B, Farre R, Dejongh S, *et al.* Intestinal barrier function in chronic kidney disease. Toxins (Basel) 2018; 10:298.
35. Terpstra ML, Singh R, Geerlings SE, *et al.* Measurement of the intestinal permeability in chronic kidney disease. World J Nephrol 2016; 5:378–388.
36. Wiedermann CJ, Kiechl S, Dunzendorfer S, *et al.* Association of endotoxemia with carotid atherosclerosis and cardiovascular disease: prospective results from the Bruneck Study. J Am Coll Cardiol 1999; 34:1975–1981.
37. Evenepoel P, Meijers BK, Bammens BR, *et al.* Uremic toxins originating from colonic microbial metabolism. Kidney Int Suppl 2009; 76(Suppl 114):S12–S19.
38. Tang WH, Wang Z, Levison BS, *et al.* Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. N Engl J Med 2013; 368: 1575–1584.
39. Kalantar-Zadeh K, Joshi S, Schlueter R, *et al.* Plant-dominant low-protein diet ■■ for conservative management of chronic kidney disease. Nutrients 2020; 12:1931.

Excellent discussion on the therapeutic potential of plant-dominant low-protein diet in chronic kidney disease (CKD).

40. Snelson M, Kellow NJ, Coughlan MT. Modulation of the gut microbiota by resistant starch as a treatment of chronic kidney diseases: evidence of efficacy and mechanistic insights. Adv Nutr 2019; 10:303–320.
41. Adair KE, Bowden RG. Ameliorating chronic kidney disease using a whole food plant-based diet. Nutrients 2020; 12:1007.
42. Koppe L, Fouque D. Microbiota and prebiotics modulation of uremic toxin generation. Panminerva Med 2017; 59:173–187.
43. Natarajan R, Pechenyak B, Vyas U, *et al.* Randomized controlled trial of strain-specific probiotic formulation (Renadyl) in dialysis patients. Biomed Res Int 2014; 2014:568571.
44. Guida B, Germano R, Trio R, *et al.* Effect of short-term synbiotic treatment on plasma p-cresol levels in patients with chronic renal failure: a randomized clinical trial. Nutr Metab Cardiovasc Dis 2014; 24:1043–1049.
45. Sumida K, Yamagata K, Kovesdy CP. Constipation in CKD. Kidney Int Rep ■ 2020; 5:121–134.

Comprehensive review discussing issues regarding constipation in CKD.

46. Joshi S, Hashmi S, Shah S, *et al.* Plant-based diets for prevention and ■ management of chronic kidney disease. Curr Opin Nephrol Hypertens 2020; 29:16–21.

Comprehensive review of the literature on plant-based diets in CKD.

47. Hamaker BR, Tuncil YE. A perspective on the complexity of dietary fiber structures and their potential effect on the gut microbiota. J Mol Biol 2014; 426:3838–3850.
48. Zimmer J, Lange B, Frick JS, *et al.* A vegan or vegetarian diet substantially alters the human colonic faecal microbiota. Eur J Clin Nutr 2012; 66:53–60.
49. Kim MS, Hwang SS, Park EJ, *et al.* Strict vegetarian diet improves the risk factors associated with metabolic diseases by modulating gut microbiota and reducing intestinal inflammation. Environ Microbiol Rep 2013; 5:765–775.
50. Chassard C, Lacroix C. Carbohydrates and the human gut microbiota. Curr Opin Clin Nutr Metab Care 2013; 16:453–460.
51. Lattimer JM, Haub MD. Effects of dietary fiber and its components on metabolic health. Nutrients 2010; 2:1266–1289.
52. Nicholson JK, Holmes E, Kinross J, *et al.* Host-gut microbiota metabolic interactions. Science 2012; 336:1262–1267.
53. Kalantar-Zadeh K, Berean KJ, Burgell RE, *et al.* Intestinal gases: influence on ■ gut disorders and the role of dietary manipulations. Nat Rev Gastroenterol Hepatol 2019; 16:733–747.

Excellent review on the profiles and modulations of intestinal gases as tools for disease prevention and therapy.

54. Kasubuchi M, Hasegawa S, Hiramatsu T, *et al.* Dietary gut microbial metabolites, short-chain fatty acids, and host metabolic regulation. Nutrients 2015; 7:2839–2849.
55. Wang HB, Wang PY, Wang X, *et al.* Butyrate enhances intestinal epithelial barrier function via up-regulation of tight junction protein Claudin-1 transcription. Dig Dis Sci 2012; 57:3126–3135.
56. Huang W, Guo HL, Deng X, *et al.* Short-chain fatty acids inhibit oxidative stress and inflammation in mesangial cells induced by high glucose and lipopolysaccharide. Exp Clin Endocrinol Diabetes 2017; 125:98–105.
57. Tan J, McKenzie C, Potamitis M, *et al.* The role of short-chain fatty acids in health and disease. Adv Immunol 2014; 121:91–119.
58. van der Beek CM, Dejong CHC, Troost FJ, *et al.* Role of short-chain fatty acids in colonic inflammation, carcinogenesis, and mucosal protection and healing. Nutr Rev 2017; 75:286–305.
59. Kieffer DA, Piccolo BD, Vaziri ND, *et al.* Resistant starch alters gut microbiome and metabolomic profiles concurrent with amelioration of chronic kidney disease in rats. Am J Physiol Renal Physiol 2016; 310:F857–F871.
60. Vaziri ND, Liu SM, Lau WL, *et al.* High amylose resistant starch diet ameliorates oxidative stress, inflammation, and progression of chronic kidney disease. PLoS One 2014; 9:e114881.
61. Lam YY, Ha CW, Hoffmann JM, *et al.* Effects of dietary fat profile on gut permeability and microbiota and their relationships with metabolic changes in mice. Obesity (Silver Spring) 2015; 23:1429–1439.
62. Fava F, Gitau R, Griffin BA, *et al.* The type and quantity of dietary fat and carbohydrate alter faecal microbiome and short-chain fatty acid excretion in a metabolic syndrome 'at-risk' population. Int J Obes (Lond) 2013; 37:216–223.
63. Kennedy A, Martinez K, Chuang CC, *et al.* Saturated fatty acid-mediated inflammation and insulin resistance in adipose tissue: mechanisms of action and implications. J Nutr 2009; 139:1–4.
64. O'Shea EF, Cotter PD, Stanton C, *et al.* Production of bioactive substances by intestinal bacteria as a basis for explaining probiotic mechanisms: bacteriocins and conjugated linoleic acid. Int J Food Microbiol 2012; 152:189–205.
65. Chen X, Wei G, Jalili T, *et al.* The associations of plant protein intake with all-cause mortality in CKD. Am J Kidney Dis 2016; 67:423–430.
66. Haring B, Selvin E, Liang M, *et al.* Dietary protein sources and risk for incident chronic kidney disease: results from the Atherosclerosis Risk in Communities (ARIC) study. J Ren Nutr 2017; 27:233–242.
67. Kim H, Caulfield LE, Garcia-Larsen V, *et al.* Plant-based diets and incident CKD and kidney function. Clin J Am Soc Nephrol 2019; 14:682–691.
68. Lin J, Hu FB, Curhan GC. Associations of diet with albuminuria and kidney function decline. Clin J Am Soc Nephrol 2010; 5:836–843.
69. Kontessis P, Jones S, Dodds R, *et al.* Renal, metabolic and hormonal responses to ingestion of animal and vegetable proteins. Kidney Int 1990; 38:136–144.
70. Kamper AL, Strandgaard S. Long-term effects of high-protein diets on renal function. Annu Rev Nutr 2017; 37:347–369.
71. Patel KP, Luo FJ, Plummer NS, *et al.* The production of p-cresol sulfate and indoxyl sulfate in vegetarians versus omnivores. Clin J Am Soc Nephrol 2012; 7:982–988.
72. Goraya N, Simoni J, Jo CH, *et al.* Treatment of metabolic acidosis in patients with stage 3 chronic kidney disease with fruits and vegetables or oral bicarbonate reduces urine angiotensinogen and preserves glomerular filtration rate. Kidney Int 2014; 86:1031–1038.
73. Goraya N, Simoni J, Jo CH, *et al.* A comparison of treating metabolic acidosis in CKD stage 4 hypertensive kidney disease with fruits and vegetables or sodium bicarbonate. Clin J Am Soc Nephrol 2013; 8:371–381.
74. Goraya N, Simoni J, Jo C, *et al.* Dietary acid reduction with fruits and vegetables or bicarbonate attenuates kidney injury in patients with a moderately reduced glomerular filtration rate due to hypertensive nephropathy. Kidney Int 2012; 81:86–93.
75. Gluba-Brzozka A, Franczyk B, Rysz J. Vegetarian diet in chronic kidney disease – a friend or foe. Nutrients 2017; 9:374.
76. Clarys P, Deliens T, Huybrechts I, *et al.* Comparison of nutritional quality of the vegan, vegetarian, semi-vegetarian, pesco-vegetarian and omnivorous diet. Nutrients 2014; 6:1318–1332.
77. Moe SM, Zidehsarai MP, Chambers MA, *et al.* Vegetarian compared with meat dietary protein source and phosphorus homeostasis in chronic kidney disease. Clin J Am Soc Nephrol 2011; 6:257–264.
78. Krishnamurthy VM, Wei G, Baird BC, *et al.* High dietary fiber intake is associated with decreased inflammation and all-cause mortality in patients with chronic kidney disease. Kidney Int 2012; 81:300–306.
79. Xu H, Huang X, Riserus U, *et al.* Dietary fiber, kidney function, inflammation, and mortality risk. Clin J Am Soc Nephrol 2014; 9:2104–2110.
80. Cupisti A, D'Alessandro C, Gesualdo L, *et al.* Non-traditional aspects of renal diets: focus on fiber, alkali and vitamin K1 intake. Nutrients 2017; 9:444.
81. Evenepoel P, Meijers BK. Dietary fiber and protein: nutritional therapy in chronic kidney disease and beyond. Kidney Int 2012; 81:227–229.
82. Rhee CM, Ahmadi SF, Kovesdy CP, *et al.* Low-protein diet for conservative management of chronic kidney disease: a systematic review and meta-analysis of controlled trials. J Cachexia Sarcopenia Muscle 2018; 9:235–245.
83. Kalantar-Zadeh K, Fouque D. Nutritional management of chronic kidney disease. N Engl J Med 2017; 377:1765–1776.
84. Cummings JH. Fermentation in the human large intestine: evidence and implications for health. Lancet 1983; 1:1206–1209.
85. Martinez AW, Recht NS, Hostetter TH, *et al.* Removal of P-cresol sulfate by hemodialysis. J Am Soc Nephrol 2005; 16:3430–3436.
86. Koeth RA, Wang Z, Levison BS, *et al.* Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat Med 2013; 19:576–585.
87. Wang Z, Klipfell E, Bennett BJ, *et al.* Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature 2011; 472:57–63.
88. Barreto FC, Barreto DV, Liabeuf S, *et al.* Serum indoxyl sulfate is associated with vascular disease and mortality in chronic kidney disease patients. Clin J Am Soc Nephrol 2009; 4:1551–1558.
89. Meijers BK, Claes K, Bammens B, *et al.* p-Cresol and cardiovascular risk in mild-to-moderate kidney disease. Clin J Am Soc Nephrol 2010; 5:1182–1189.
90. Stubbs JR, House JA, Ocque AJ, *et al.* Serum trimethylamine-*N*-oxide is elevated in CKD and correlates with coronary atherosclerosis burden. J Am Soc Nephrol 2016; 27:305–313.

91. Tang WH, Wang Z, Kennedy DJ, *et al.* Gut microbiota-dependent trimethylamine-*N*-oxide (TMAO) pathway contributes to both development of renal insufficiency and mortality risk in chronic kidney disease. Circ Res 2015; 116:448–455.

92. Black AP, Anjos JS, Cardozo L, *et al.* Does low-protein diet influence the uremic toxin serum levels from the gut microbiota in nondialysis chronic kidney disease patients? J Ren Nutr 2018; 28:208–214.

93. ■ Lai S, Molfino A, Testorio M, *et al.* Effect of low-protein diet and inulin on microbiota and clinical parameters in patients with chronic kidney disease. Nutrients 2019; 11:3006.

An important article highlighting the effect of low-protein diet on gut microbiota in CKD.

94. Dhar D, Mohanty A. Gut microbiota and Covid-19-possible link and implications. Virus Res 2020; 285:198018.

95. Glennas A, Brath HK, Bergaust B. Ocular side effects of chloroquine treatment of rheumatoid arthritis patients. Tidsskr Nor Laegeforen 1980; 100:902–903.

96. McFarlane C, Ramos CI, Johnson DW, *et al.* Prebiotic, probiotic, and synbiotic supplementation in chronic kidney disease: a systematic review and meta-analysis. J Ren Nutr 2019; 29:209–220.

97. Rossi M, Johnson DW, Morrison M, *et al.* Synbiotics easing renal failure by improving gut microbiology (SYNERGY): a randomized trial. Clin J Am Soc Nephrol 2016; 11:223–231.

98. Meijers BK, De Preter V, Verbeke K, *et al.* p-Cresyl sulfate serum concentrations in haemodialysis patients are reduced by the prebiotic oligofructose-enriched inulin. Nephrol Dial Transplant 2010; 25:219–224.

99. Sumida K, Molnar MZ, Potukuchi PK, *et al.* Constipation and incident CKD. J Am Soc Nephrol 2017; 28:1248–1258.

100. Sumida K, Molnar MZ, Potukuchi PK, *et al.* Constipation and risk of death and cardiovascular events. Atherosclerosis 2019; 281:114–120.

101. Zhao Y, Yu YB. Intestinal microbiota and chronic constipation. Springerplus 2016; 5:1130.

102. Khalif IL, Quigley EM, Konovitch EA, *et al.* Alterations in the colonic flora and intestinal permeability and evidence of immune activation in chronic constipation. Dig Liver Dis 2005; 37:838–849.

103. Simren M, Barbara G, Flint HJ, *et al.* Intestinal microbiota in functional bowel disorders: a Rome foundation report. Gut 2013; 62:159–176.

104. Parthasarathy G, Chen J, Chen X, *et al.* Relationship between microbiota of the colonic mucosa vs feces and symptoms, colonic transit, and methane production in female patients with chronic constipation. Gastroenterology 2016; 150:367–379.e1.

105. Barbara G, Stanghellini V, Brandi G, *et al.* Interactions between commensal bacteria and gut sensorimotor function in health and disease. Am J Gastroenterol 2005; 100:2560–2568.

106. Triantafyllou K, Chang C, Pimentel M. Methanogens, methane and gastrointestinal motility. J Neurogastroenterol Motil 2014; 20:31–40.

107. Bharucha AE, Pemberton JH, Locke GR 3rd. American Gastroenterological Association technical review on constipation. Gastroenterology 2013; 144:218–238.

108. De Schryver AM, Samsom M, Smout AI. Effects of a meal and bisacodyl on colonic motility in healthy volunteers and patients with slow-transit constipation. Dig Dis Sci 2003; 48:1206–1212.

109. Muller-Lissner SA, Kamm MA, Scarpignato C, *et al.* Myths and misconceptions about chronic constipation. Am J Gastroenterol 2005; 100:232–242.

110. Suares NC, Ford AC. Systematic review: the effects of fibre in the management of chronic idiopathic constipation. Aliment Pharmacol Ther 2011; 33:895–901.

111. Sumida K, Dashputre AA, Potukuchi PK, *et al.* Laxative use in patients with advanced chronic kidney disease transitioning to dialysis. Nephrol Dial Transplant 2020. doi: 10.1093/ndt/gfaa205. Online ahead of print.

112. Tayebi-Khosroshahi H, Habibzadeh A, Niknafs B, *et al.* The effect of lactulose supplementation on fecal microflora of patients with chronic kidney disease: a randomized clinical trial. J Renal Inj Prev 2016; 5:162–167.

113. Sueyoshi M, Fukunaga M, Mei M, *et al.* Effects of lactulose on renal function and gut microbiota in adenine-induced chronic kidney disease rats. Clin Exp Nephrol 2019; 23:908–919.

114. Mishima E, Fukuda S, Shima H, *et al.* Alteration of the intestinal environment by lubiprostone is associated with amelioration of adenine-induced CKD. J Am Soc Nephrol 2015; 26:1787–1794.

115. Nanto-Hara F, Kanemitsu Y, Fukuda S, *et al.* The guanylate cyclase C agonist linaclotide ameliorates the gut-cardio-renal axis in an adenine-induced mouse model of chronic kidney disease. Nephrol Dial Transplant 2019; 35:250–264.

116. Brugere JF, Mihajlovski A, Missaoui M, *et al.* Tools for stools: the challenge of assessing human intestinal microbiota using molecular diagnostics. Expert Rev Mol Diagn 2009; 9:353–365.

117. Grice EA. The skin microbiome: potential for novel diagnostic and therapeutic approaches to cutaneous disease. Semin Cutan Med Surg 2014; 33:98–103.

118. Lane DJ, Pace B, Olsen GJ, *et al.* Rapid determination of 16S ribosomal RNA sequences for phylogenetic analyses. Proc Natl Acad Sci U S A 1985; 82:6955–6959.

119. Findley K, Oh J, Yang J, *et al.* Topographic diversity of fungal and bacterial communities in human skin. Nature 2013; 498:367–370.

120. Emerich DF, Thanos CG. Nanotechnology and medicine. Expert Opin Biol Ther 2003; 3:655–663.

121. Weiss PS. Opportunities for nanoscience and nanotechnology in studying microbiomes. ACS Nano 2016; 10:1–2.

122. Biteen JS, Blainey PC, Cardon ZG, *et al.* Tools for the microbiome: nano and beyond. ACS Nano 2016; 10:6–37.

123. Nakhleh MK, Amal H, Jeries R, *et al.* Diagnosis and classification of 17 diseases from 1404 subjects via pattern analysis of exhaled molecules. ACS Nano 2017; 11:112–125.

124. Kalantar-Zadeh K, Ha N, Ou JZ, *et al.* Ingestible sensors. ACS Sens 2017; 2:468–483.

125. Singh T, Shukla S, Kumar P, *et al.* Application of nanotechnology in food science: perception and overview. Front Microbiol 2017; 8:1501.

126. Hua S, Marks E, Schneider JJ, *et al.* Advances in oral nano-delivery systems for colon targeted drug delivery in inflammatory bowel disease: selective targeting to diseased versus healthy tissue. Nanomedicine 2015; 11:1117–1132.

127. Kalantar-Zadeh K, Ward SA, Kalantar-Zadeh K, *et al.* Considering the effects of microbiome and diet on SARS-CoV-2 infection: nanotechnology roles. ACS Nano 2020; 14:5179–5182.

128. Guo L, McLean JS, Yang Y, *et al.* Precision-guided antimicrobial peptide as a targeted modulator of human microbial ecology. Proc Natl Acad Sci U S A 2015; 112:7569–7574.

129. Eckert R, He J, Yarbrough DK, *et al.* Targeted killing of Streptococcus mutans by a pheromone-guided 'smart' antimicrobial peptide. Antimicrob Agents Chemother 2006; 50:3651–3657.

130. Prakash S, Chang TM. Microencapsulated genetically engineered live *E. coli* DH5 cells administered orally to maintain normal plasma urea level in uremic rats. Nat Med 1996; 2:883–887.