The Gut Microbiome, Kidney Disease, and Targeted Interventions

Ali Ramezani and Dominic S. Raj
Division of Renal Diseases and Hypertension, The George Washington University, Washington DC

ABSTRACT

The human gut harbors >100 trillion microbial cells, which influence the nutrition, metabolism, physiology, and immune function of the host. Here, we review the quantitative and qualitative changes in gut microbiota of patients with CKD that lead to disturbance of this symbiotic relationship, how this may contribute to the progression of CKD, and targeted interventions to re-establish symbiosis. Endotoxin derived from gut bacteria incites a powerful inflammatory response in the host organism. Furthermore, protein fermentation by gut microbiota generates myriad toxic metabolites, including p-cresol and indoxyl sulfate. Disruption of gut barrier function in CKD allows translocation of endotoxin and bacterial metabolites to the systemic circulation, which contributes to uremic toxicity, inflammation, progression of CKD, and associated cardiovascular disease. Several targeted interventions that aim to re-establish intestinal symbiosis, neutralize bacterial endotoxins, or adsorb gut-derived uremic toxins have been developed. Indeed, animal and human studies suggest that prebiotics and probiotics may have therapeutic roles in maintaining a metabolically-balanced gut microbiota and reducing progression of CKD and uremia-associated complications. We propose that further research should focus on using this highly efficient metabolic machinery to alleviate uremic symptoms.


GUT MICROBIOTA: AN ENDOGENOUS ORGAN

The human gut harbors a complex community of >100 trillion microbial cells that constitute the gut microbiota. The combined microbial genome of the gut microbiota is known as the gut microbiome. In general, the adult gut is dominated by two bacterial phyla, Firmicutes and Bacteroidetes; other phyla, including Actinobacteria, Proteobacteria, Verrucomicrobia, Cyanobacteria, Fusobacteria, Spirochaetes, and TM7, are present in smaller proportions. Each species of bacteria colonizes a specific niche, leading to different bacterial composition along the intestinal tract (Table 1). Gut microbiota performs a multitude of functions and can be considered a metabolically active endogenous “organ” in itself. Under physiologic conditions, it participates in certain complementary metabolic activities that have not been fully evolved in the human host, such as breakdown of undigestible plant polysaccharides, synthesis of certain vitamins, biotransformation of conjugated bile acids, and degradation of dietary oxalates. Importantly, postnatal colonization of the intestine educates our immune system and reduces allergic responses to food and environmental antigens.

The utility of human gut microbiota in the diagnosis, treatment, and prevention of disease requires a clear understanding of its composition, dynamics, and stability within an individual. A recent study aimed at characterizing the long-term stability of the human gut microbiota used low-error amplicon sequencing of fecal samples from 37 healthy adults collected over a period of 296 weeks. The results revealed that on average, the microbiota was remarkably stable over time within an individual and between family members but not between unrelated individuals. These
findings further emphasize the importance of the early gut colonizers, such as those acquired from parents and siblings, and their potential life-long effect on our health and disease.

**Microbiota-Host Signaling**

Mammalian gut microbiota forms a complex ecosystem that requires proper interaction with its host for symbiotic benefits. One of the best examples of the microbiota-host signaling is the host immunomodulation by *Bacteroides fragilis* polysaccharide A molecule, which directs the maturation of the developing immune system by mediating establishment of a proper T-helper cell (TH1/TH2) balance. The gut microbiota can also sense host-produced molecules. For instance, norepinephrine released in response to stress could increase the growth and production of virulence-associated factors of Gram-negative bacteria. Finally, different members of the gut microbiota also communicate for establishment or maintenance of homeostasis in the intestinal ecosystem. When germ-free mice were colonized with *Bacteroides thetaiotaomicron* and *Methanobrevibacter smithii*, the latter directed *B. thetaiotaomicron* to focus on fermentation of dietary fructans to acetate, whereas *B. thetaiotaomicron*-derived formate was used by *M. smithii* for methanogenesis.

**Intestinal Epithelial Barrier**

In addition to allowing absorption of nutrients, the intestinal epithelium also functions as a barrier to prevent systemic translocation of antigens and pathogens (Figure 2A). The intestinal epithelium is a single layer of columnar epithelial cells that separates the intestinal lumen from the underlying lamina propria. These epithelial cells are bound together by tight junctions, making a multifunctional complex that forms a seal between adjacent epithelial cells. Commensal gut microbes maintain functional integrity of gut by several mechanisms, including restoration of tight junction protein structure, induction of epithelial heat-shock proteins, upregulation of mucin genes, competition with pathogenic bacteria for binding to intestinal epithelial cells, and secretion of antimicrobial peptides. Probiotic bacteria enhance intestinal epithelial barrier function in murine models of colitis and in patients with Crohn disease. Treating human epithelial cell monolayers with metabolites secreted by *Bifidobacterium infantis* causes an increase in tight junction proteins ZO-1 and occludin while reducing claudin-2, thus demonstrating the ability of bacteria and bacterial products to modify ion permeability and selectivity of tight junction. In germ-free mice, colonization with *B. thetaiotaomicron* resulted in modulation in expression of genes involved in several important intestinal functions.

Commensal bacteria also play an important role in maintaining the intestinal epithelial barrier by suppressing intestinal inflammation. Toll-like receptors (TLRs) comprise a family of pattern-recognition receptors that detect conserved molecular products of microorganisms, such as LPS and lipoteichoic acid, recognized by TLR4 and TLR2, respectively. TLR2 stimulation effectively preserved tight junction-associated barrier assembly against stress-induced damage through promotion of phosphatidylinositol 3-kinase/protein kinase B-mediated cell survival via myeloid differentiation factor 88 (MyD88). Microbiota signaling through mucosal TLRs was also shown to be required for maintenance of intestinal epithelial homeostasis and repair following intestinal injury.
GUT MICROBIOTA IN OBESITY AND INSULIN RESISTANCE

Data from the US Renal Data System shows an epidemic of obesity among the ESRD population. Insulin resistance is common in patients with CKD and is in part due to a high prevalence of shared risk factors, such as obesity and sedentary lifestyle. Recent findings suggest that our gut microbiota might be involved in the development of obesity and related disorders, such as insulin resistance. Weight gain is associated with an increase in the capacity of the microbiota to extract nutrients from the diet and in inducing metabolic changes in the host, such as increased fatty acid oxidation in muscle and increased triglyceride storage in the liver. Germ-free mice ingesting a high-fat diet do not gain weight or develop adiposity; however, reconstitution of germ-free mice gut with microbiota from lean mice or from genetically or diet-induced obese mice causes weight gain. Gut microbiota composition is significantly different in genetically obese mice and obese patients compared with lean controls. A high-fat (Western) diet modifies the gut microbiota by reducing the relative abundance of Bacteroidetes and increasing the relative abundance of Firmicutes. An increase of genes involved in the import and processing of sugars in the gut metagenome was also found in mice fed with Western diet.

The role of the gut microbiota in type 1 and 2 diabetes has been researched in mouse models. The development of type 1 diabetes in MyD88-deficient nonobese diabetic (NOD) mice depended on the presence or absence of the gut microbiota, and nearly all germ-free MyD88-deficient NOD mice developed diabetes, whereas colonization of these germ-free MyD88-deficient NOD mice with a defined gut microbiota (representing bacterial phyla normally present in human gut) attenuated type 1 diabetes. Another study compared the fecal microbiota profile in lean control, obese diabetic, and obese nondiabetic participants and noted that diabetes was associated with a reduction of Faecalibacterium prausnitzii species. A case-control study of type 2 patients with diabetes found decreased Bacteroides vulgatus and Bifidobacterium genus in the diabetic group compared with a healthy control group. Thus, altered gut microbiota could play an important role in the development of obesity, insulin resistance, and diabetes.

INTESTINAL DYSBIOSIS IN CKD/ESRD

Gut Microbiome in CKD/ESRD

Uremic patients show greatly increased counts of both aerobic (approximately 10^6 bacteria/ml) and anaerobic (approximately 10^7 bacteria/ml) organisms in the
Figure 2. (A) Intestinal epithelial barrier and inflammatory responses in symbiotic and dysbiotic gut microbiota. A symbiotic gut microbiota leads to development of a functional barrier, with normal amounts of mucus, pattern recognition receptors (PRRs), antimicrobial peptides (AMPs), and secreted IgA, which in turn contain the microbiota in the intestinal lumen and away from the intestinal epithelial cells. As a result, the intestinal immune system becomes largely tolerant to the resident commensals. Similar to immune cells, the signaling cascades that occur downstream of TLRs (enlarged on the left) are used by epithelial cells to detect microbes through PRRs, such as the TLR4. Briefly, upon LPS ligation, the MYD88 is recruited, which activates the NF-κB pathway and leads to production of antimicrobial proteins and proinflammatory cytokines. In a symbiotic gut, epithelial cells are desensitized by continuous exposure to LPS or are attenuated by (1) LPS-mediated downregulation of the IL-1 receptor–associated kinase 1 (IRAK1), which is the proximal activator of the NF-κB cascade; (2) LPS-mediated induction of peroxisome proliferator-activated receptor-γ (PPARγ), which can divert NF-κB from the nucleus; or (3) commensal bacteria-derived reactive oxygen species (ROS)–mediated inhibition of polyubiquitylation and degradation of the aortic inhibitor of NF-κB. (T bars indicate the checkpoints that are controlled by the microbiota.) Exposure to LPS induces epithelial cells to secrete TGF-β, B-cell–activating factor of the TNF family (BAFF), and a proliferation-inducing ligand (APRIL), all promoting the development of tolerant immune responses to the microbiota. CD103+ dendritic cells (DCs) support the development of regulatory T (Treg) cells secreting IL-10 and TGF-β, and together they stimulate the production of commensal-specific IgA. Increased intestinal concentration of uremic toxins associated with the progression of CKD leads to microbial dysbiosis and overgrowth of pathobionts. Pathobiont overgrowth leads to the loss of barrier integrity and the breach in the epithelia barrier. Translocation of bacteria and bacterial components triggers the intestinal immune system to direct a potentially harmful proinflammatory response to clear invading bacteria by secreting IL-1 and -6 from intestinal epithelial cells, promoting a Th1 and Th17 response by DCs and macrophages and producing higher levels of commensal-specific IgG by B cells. In this context, LPS binding to its receptor complex on macrophages (enlarged on the left) results in enhanced production of inflammatory cytokines including IFN-β, IFN-γ, IL-1β, IL-6, TNFα, and IL-12, the production of which has been shown to require activation of p38MAPK. Subclinical endotoxemia is a potential cause of inflammation in CKD. Dysregulated immune response and chronic production of proinflammatory cytokines lead to systemic inflammation, which could further accelerate the progression of CKD and development of cardiovascular disease. IkB, inhibitor of NF-κB.
duodenum and jejunum, normally not colonized heavily by bacteria in healthy persons (Table 1). Lower intestinal microbial flora has also been shown to be altered in patients with CKD, most notably with decreases in both Lactobacillaceae and Prevotellaceae families. Hida et al. studied the colonic composition of microbiota in healthy controls and hemodialysis patients. Analysis of the fecal microbiota revealed a disturbed composition of the microbiota characterized by an overgrowth of aerobic bacteria. Although this study did not show a significant difference in the total number of bacteria, the number of aerobic bacteria, such as Enterobacteria and Enterococci species, was approximately 100 times higher in hemodialysis patients. Of the anaerobic bacteria, hemodialysis patients had significantly lower numbers of Bifidobacteria and higher Clostridium perfringens. Patients with ESRD were also at a high risk of Clostridium difficile–associated diarrheas. Vaziri et al. showed significant differences in the abundance of 190 microbial operational taxonomic units (OTUs) between the patients with ESRD and the normal control individuals. To isolate the effect of renal failure, the investigators also examined the gut microbiota in nephrectomized rats. The study revealed substantially lower species richness as measured by the number of operational taxonomic units in the nephrectomized rats compared with the controls.

The intestinal dysbiosis may be due to iatrogenic causes or uremia per se. Loss of kidney function leads to secretion of urea into the gastrointestinal tract. Subsequent hydrolysis of urea by urease expressed by some gut microbes, results in the formation of large quantities of ammonia, which could affect the growth of commensal bacteria. Other contributing factors include decreased consumption of dietary fiber, frequent use of antibiotics, slow colonic transit, metabolic acidosis, intestinal wall edema, and possibly oral iron intake.

There is high prevalence of insufficiency or deficiency in vitamin K among patients with CKD and ESRD. Pioneering work of Almquist and Stokstad has recognized the biosynthesis of vitamin K by intestinal bacteria as an important source in animals and humans. Investigators have shown that certain strains, such as B. fragilis, Bifidobacteria...
species, Clostridia species, and Streptococcus faecalis, are involved in the biosynthesis of vitamin K. The lower part of the intestinal tract, where the bacterial density is highest, is most likely site for the absorption of the vitamin. Consistent with these findings, the intestinal flora has been associated with symptomatic vitamin K deficiency and severe hemorrhage.

**Gut Barrier Function in CKD**

The gastrointestinal system is at the interphase between the blood and the potentially toxic contents of the gut. Histologic changes, including reduction of villous height, elongation of the crypts, and infiltration of lamina propria with inflammatory cells are noted in CKD (Figure 2B). Uremia increases intestinal permeability, both in uremic rats and in patients with CKD. The disruption of colonic epithelial tight junction could subsequently lead to translocation of bacteria and endotoxin across the intestinal wall. Studies in uremic rats have shown marked azotemia, systemic oxidative stress, and marked depletion of the key protein constituents of the epithelial tight junction (claudin-1, occludin, and ZO1) in the stomach, jejunum, and ileum, as well as penetration of bacteria across the intestinal wall and localization in the mesenteric lymph nodes. Hemodialysis-induced systemic circulatory stress and recurrent regional ischemia may also damage the mechanical barrier of the gut. In addition, factors that promote intestinal dysbiosis may also contribute to the leaky gut in CKD. Gut microbiome dysbiosis is associated with bacterial translocation, thereby contributing to microinflammation in experimental uremia as well as in patients with ESRD.

**Endotoxin as a Cause of Inflammation in CKD**

Endotoxin, the hydrophobic anchor of LPS, is a phospholipid that constitutes the outer membranes of most Gram-negative bacteria. It is continuously produced in the gut and is transported into intestinal capillaries through a TLR4-dependent mechanism. Endotoxin circulates in the plasma of healthy humans at low concentrations (between 1 and 200 pg/ml). It is taken up by liver and mononuclear phagocyte cells and eventually cleared. Endotoxin provokes an array of host responses by binding to the 55-kD glycosyl-phosphatidyl-inositol-anchored myeloid differentiation antigen, CD14. LPS-binding protein is a key modulator of cellular response to endotoxin. Endotoxin stimulates cells of the immune system, particularly macrophages and the endothelial cells, to become activated and to synthesize and secrete a variety of effector molecules that cause an inflammatory response. Recent evidence indicates that subclinical endotoxemia is a potential cause for inflammation in patients with CKD.

**Endotoxin and Atherosclerosis**

The association between bacteria and atherosclerosis has been known for more than two decades. Recently, focus has shifted from bacteria to its product, endotoxin, for its role in the development of atherosclerosis. Endotoxin is a key factor in initiation and progression of atherosclerosis through mediation of endothelial cell injury, promotion of recruitment of monocytes, transformation of macrophages to foam cells, and procoagulant activity. Furthermore, vascular smooth muscle cells exhibit profound responsiveness to even very low levels of endotoxin. The Bruneck study showed that elevated endotoxin level is a strong risk factor for the development of atherosclerosis in the general population. Elevated plasma level of sCD14 is noted in patients with unstable angina and is related to increased aortic stiffness and carotid plaque formation. The Bruneck study showed that circulating endotoxia in patients undergoing peritoneal dialysis is related to systemic inflammation and features of atherosclerosis. Using two separate cohorts, we demonstrated that sCD14 is associated with mortality in patients with ESRD.

**Gut-Derived Uremic Toxins**

Certain intestinal bacteria can generate uremic toxins that are absorbed into the blood and are normally cleared by the kidney. Protein fermentation by gut microbiota results in the generation of different metabolites, including phenols and indoles. Aronov et al. compared plasma from hemodialysis patients with and without colon and confirmed the colonic origin of indoxyl sulfate and p-cresol. These are prototype members of a large group of protein-bound uremic toxins that are resistant to clearance by dialysis. P-cresol, a 108-Da protein-bound solute, is a colonic fermentation product of the amino acid tyrosine and phenylalanine. Most of the p-cresol generated by the intestinal flora is conjugated to p-cresyl sulfate in the intestinal wall and to p-cresyl glucuronide in the liver. Intestinal bacteria also have tryptophanase that converts tryptophan to indole, which is subsequently absorbed and metabolized to indoxyl sulfate in the liver.

Concentrations of indoxyl sulfate and p-cresyl sulfate in the serum are negatively correlated with the level of kidney function. A prospective, observational study performed in 268 patients with CKD indicated that baseline levels of indoxyl sulfate and p-cresyl sulfate were predictors of CKD progression. Animal studies suggest that these uremic toxins may damage renal tubular cells. In uremic rats, administration of indoxyl sulfate mediates the renal expression of genes related to tubulointerstitial fibrosis, such as TGF-β1, tissue inhibitor of metalloproteinases, and pro-α 1, accompanied by a significant decline in renal function and worsening of glomerular sclerosis. Indoxyl sulfate also induces nephrotoxicity via organic anion transporter–mediated uptake in the basolateral membrane of renal proximal tubular cells, where it activates NF-κB and plasminogen activator inhibitor type 1 expression. Barreto et al. showed that an elevated level of indoxyl sulfate is associated with vascular stiffness, aortic calcification, and higher cardiovascular mortality. Indoxyl sulfate is a potential vascular toxin that induces oxidative stress in endothelial cells, increases shedding of endothelial microparticles, impairs endothelial cell...
repair mechanism,\textsuperscript{116} and increases vascular smooth muscle cell proliferation.\textsuperscript{117} Bammens \textit{et al.}\textsuperscript{118} reported that free serum levels of p-cresol is associated with mortality in hemodialysis patients. \textit{In vitro} evidence indicates that p-cresol inhibits cytokine-stimulated expression of endothelial adhesion molecules—intercellular adhesion molecule 1 and vascular cell adhesion molecule \textsuperscript{119}—and induces increase in endothelial permeability.\textsuperscript{120} Thus, gut-derived uremic toxins contribute to progression of CKD as well as cardiovascular disease.

**TARGETED INTERVENTIONS TO TREAT INTESTINAL DYSBIOSIS**

Recent advances in our understanding of the gut microbiome’s physiologic functions and pathologic consequences of dysbiosis have led to exploration of various ways of reestablishing symbiosis. Most therapies targeting the colonic microenvironment in CKD aim to modulate gut microbiota, block LPS or attenuate inflammation, or target adsorption of uremic toxin end products of microbial fermentation. Some of these approaches are briefly discussed below (reviewed in Table 2).

**Modulation of Gut Microbiota**

**Prebiotics**

A prebiotic is a nondigestible (by the host) food ingredient that has a beneficial effect through its selective stimulation of the growth or activity of one or a limited number of bacteria in the colon.\textsuperscript{121,122} The candidate prebiotics include inulin, fructo-oligosaccharides, galacto-oligosaccharides, soya-oligosaccharides, xylo-oligosaccharides, and pyrodictins. Prebiotics promote the growth of \textit{Bifidobacteria} and \textit{Lactobacilli} species at the expense of other groups of bacteria in the gut, such as \textit{Bacteroides} species, \textit{Clostridia} species, and enterobacteria.\textsuperscript{123} Preliminary evidence indicates that prebiotic oligofructose-enriched inulin (p-inulin) promotes growth of \textit{Bifidobacteria} species, mediates weight loss, reduces inflammation, and improves metabolic function.\textsuperscript{124–126} High dietary fiber intake is associated with lower risk of inflammation and reduced mortality in patients with CKD.\textsuperscript{127} Meijsers \textit{et al.}\textsuperscript{128} reported that serum concentrations of p-cresol and indoxyl sulfate are reduced by the oral intake of p-inulin in hemodialysis patients.

One of the mechanisms by which p-inulin mediates weight loss may be by enhancing satiety due to bacterial fermentation and increased production of short-chain fatty acids in the gut lumen.\textsuperscript{126} Short-chain fatty acids stimulate secretion of glucagon-like peptide 1 (GLP-1)\textsuperscript{129} and peptide YY (PYY).\textsuperscript{130} GLP-1 has antiobesity and antidiabetic actions by such mechanisms as inhibiting food intake, stimulating insulin secretion, and inducing B-cell proliferation.\textsuperscript{131} PYY colocalizes with GLP-1 in the intestinal L cells and is also considered an anorexigenic peptide.\textsuperscript{132} Plasma concentrations of GLP-1\textsuperscript{133} and PYY\textsuperscript{134} are reduced in obese individuals, and oligofructose supplementation in rats resulted in reductions in energy intake and increased plasma GLP-1 and PYY concentrations.\textsuperscript{135}

**Probiotics**

Probiotics are defined by the United Nations’ Food and Agriculture Organization and the World Health Organization as “live microorganisms” that when administered in adequate amounts confer a health benefit on the host.\textsuperscript{136} Probiotics consist of living bacteria, such as \textit{Bifidobacteria} species, lactobacilli, and streptococci,\textsuperscript{137} that can alter gut microbiota and affect the inflammatory state.\textsuperscript{138,139} Treatment with \textit{Bacillus pasteurii} and Sporlac slowed the progression of kidney disease and prolonged the life span of fifth/sixth nephrectomized Sprague-Dawley rats.\textsuperscript{140} Hemodialysis patients treated with oral \textit{Lactobacillus acidophilus} showed decreased serum dimethylamine, a potential uremic toxin.\textsuperscript{10} In another study, treatment with \textit{L. acidophilus} ATCC-4356 reduced the atherosclerotic burden in ApoE\textsuperscript{−/−} mice.\textsuperscript{141} This was accompanied by an inhibition of translocation of NF-kB p65 from cytoplasm to nucleus, suppression of degradation of aortic inhibitor of NF-kB α, and improvements in gut microbiota distribution. Prakash \textit{et al.}\textsuperscript{142} reduced BUN in uremic rats by orally administering microencapsulated, genetically engineered live cells that contained living urease-producing \textit{Escherichia coli}–DH5.

**Acarbose**

Acarbose is an inhibitor of α-glucosidase enzymes in the intestinal brush-border that blocks the hydrolysis of poly- and oligosaccharides to glucose and other monosaccharides. The undigested oligosaccharides that enter the colon act as fermentable carbohydrates. Evenepoel \textit{et al.}\textsuperscript{143} showed that treatment with acarbose reduces the colonic generation of p-cresol in healthy persons.

**Gut Microbiome Transplantation**

Manichanh \textit{et al.}\textsuperscript{144} examined the long-term effects of exogenous microbiota transplantation alone and combined with antibiotic pretreatment in a rat model. A short intake of antibiotics produced profound long-term effects on the rat intestinal microbiome, with reduced gut microbial diversity. Transplantation of a rich pool of exogenous bacteria led to an increase in bacterial diversity and changing the microbiome of the recipients to resemble that of the donor. Human fecal transplantation has demonstrated efficacy against \textit{Clostridium difficile} colitis.\textsuperscript{145}

**Essential Oils**

The potential of essential oils as agents to treat dysbiosis was examined in an \textit{in vitro} study.\textsuperscript{146} Results indicated that \textit{Carum carvi}, \textit{Lavandula angustifolia}, \textit{Trachyspermum copticum}, and \textit{Citrus aurantium var. amara} essential oils displayed the greatest degree of selectivity, inhibiting the growth of potential pathogens at concentrations that had no effect on the beneficial bacteria examined.\textsuperscript{146} More research is needed, however, to evaluate tolerability and safety concerns and to verify the selective action of these agents.

**Blocking of LPS/Attenuation of Inflammation**

**Sevelamer**

Sevelamer is a large cationic polymer phosphate binder that binds endotoxin in...
both in vitro and in vivo studies. A cross-sectional study in hemodialysis patients showed that endotoxin level was lower in patients using sevelamer. Subsequently, a prospective, randomized, open-label study further confirmed that treatment with sevelamer reduced endotoxin and sCD14 levels in hemodialysis patients. Potential interaction between sevelamer and fat-soluble vitamins, including vitamin A, D, E, and K, has been proposed but remains to be determined.

**Synthetic TLR4 Antagonists**

The biologic activity of LPS resides almost entirely in its lipid A component. The synthetic lipid A analogue eritoran (E5564) and the lipid A mimetic CRX-5261 inhibit LPS signaling. In healthy persons, E5564 blocked all of the effects of LPS, with significant reductions in white blood cell count, C-reactive protein levels, and cytokine levels (TNF-α and IL-6). More recently, C34, a 2-acetamidopyranoside, was developed. It inhibited TLR4 in enterocytes

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**Table 2. Effect of probiotics and prebiotics on uremic toxins, inflammation, and atherosclerosis**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient Type/Model (number)</th>
<th>Intervention</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Uremic toxins&lt;br&gt;Simenhoff et al.10</td>
<td>HD patients (8)</td>
<td>L. acidophilus</td>
<td>↓ Serum dimethylamine&lt;br&gt;↓ Nitrosodimethylamine</td>
</tr>
<tr>
<td>Prakash et al.142</td>
<td>Uremic rats</td>
<td>Genetically engineered E. coli</td>
<td>↓ Plasma urea</td>
</tr>
<tr>
<td>Ranganathan et al.173</td>
<td>Nephrectomized rats</td>
<td>Various combinations of probiotics</td>
<td>↑ Lifespan&lt;br&gt;↑ BUN&lt;br&gt;↑ Uric acid concentration&lt;br&gt;↑ BUN</td>
</tr>
<tr>
<td>Ranganathan et al.174</td>
<td>Patients with CKD (13)</td>
<td>S. thermophilus, L. acidophilus, and B. longum</td>
<td>↓ Serum p-cresyl sulfate and generation rate&lt;br&gt;↓ Urinary excretion of p-cresol&lt;br&gt;↓ Serum p-cresyl sulfate</td>
</tr>
<tr>
<td>Ranganathan et al.175</td>
<td>Patients with CKD (246)</td>
<td>S. thermophilus, L. acidophilus, and B. longum</td>
<td>↓ Fecal protein catabolites (beneficial) with fructooligosaccharides&lt;br&gt;↑ Fecal protein catabolites (harmful) with L. acidophilus</td>
</tr>
<tr>
<td>Meijers et al.128</td>
<td>HD patients (22)</td>
<td>Oligofructose-enriched inulin</td>
<td>↓ Fecal protein catabolites (beneficial) with fructooligosaccharides&lt;br&gt;↑ Fecal protein catabolites (harmful) with L. acidophilus</td>
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<tr>
<td>de Preter et al.176</td>
<td>Healthy persons (50)</td>
<td>Oligofructose-enriched inulin</td>
<td>↓ Fecal protein catabolites (beneficial) with fructooligosaccharides&lt;br&gt;↑ Fecal protein catabolites (harmful) with L. acidophilus</td>
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<tr>
<td>Nakabayashi et al.177</td>
<td>HD patients (7)</td>
<td>Galacto-oligosaccharides, L. casei, and B. breve</td>
<td>↓ Fecal protein catabolites (beneficial) with fructooligosaccharides&lt;br&gt;↑ Fecal protein catabolites (harmful) with L. acidophilus</td>
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<td>Swanson et al.178</td>
<td>Healthy persons (68)</td>
<td>Fructooligosaccharides and/or L. acidophilus</td>
<td>↓ Fecal protein catabolites (beneficial) with fructooligosaccharides&lt;br&gt;↑ Fecal protein catabolites (harmful) with L. acidophilus</td>
</tr>
</tbody>
</table>

Atherosclerosis<br>Chen et al.141 | ApoE−/− mice | L. acidophilus | ↓ Atherosclerotic burden<br>↓ Atherosclerotic lesions |
| Uchida et al.179 | Rabbits on a high cholesterol diet | Exopolysaccharide | ↓ Reperfusion tachyarrhythmia<br>↑ Functional recovery of the ischemic rat hearts<br>↓ Norepinephrine release |
| Oxman et al.180 | Sprague-Dawley rats | L. bulgaricus-51 | ↓ Atherosclerotic burden<br>↓ Atherosclerotic lesions |
| Naruszewicz et al.181 | Healthy persons (36) | L. plantarum 299v | ↓ Systolic BP and fibrinogen<br>↓ F₂-Isoprostanes and IL-6<br>↓ Monocyte adhesion to endothelial cells |

Inflammation<br>Neyrinck et al.182 | Mice | High-molecular-weight arabinoyxylane | ↑ Bifidobacteria<br>↓ Inflammation |
| Cani et al.124 | Mice | Oligofructose | ↓ Endotoxemia and proinflammatory cytokines |
| Dewulf et al.183 | Obese women (30) | Inulin/oligofructose | ↓ Endotoxemia<br>Preserved insulin sensitivity<br>↓ Inflammation |
| Andreassen et al.184 | Patients with T2DM (45) | L. acidophilus NCFM75 | ↓ TNF-α and IL-6 mRNAs<br>↓ Serum sCD14 |
| Schiffrin et al.185 | Elderly persons (74) | Oligosaccharides | ↓ Preserved insulin sensitivity<br>Did not affect systemic inflammation |
| Andreassen et al.184 | Patients with T2DM (45) | L. acidophilus | ↓ Rate of systemic inflammatory response, syndrome, infections, severe sepsis, and mortality |
| Anderson et al.186 | Elective surgical patients (137) | Combination of probiotics | ↑ Preserved insulin sensitivity<br>↑ Fecal protein catabolites (beneficial) with fructooligosaccharides<br>↓ Fecal protein catabolites (harmful) with L. acidophilus |
| Kotzampassi et al.187 | Trauma patients | Probiotics along with and inulin, oat bran, pectin, and resistant starch | ↓ Rate of systemic inflammatory response, syndrome, infections, severe sepsis, and mortality |

HD, hemodialysis; T2DM, type 2 diabetes mellitus.
and macrophages in vitro and reduced systemic inflammation in mouse models of endotoxemia and necrotizing enterocolitis.156

**Adsorption of Uremic Toxins**

**Oral Adsorbents**

AST-120 is an oral adsorbent consisting of microspheres made from porous carbon material. Administration of AST-120 partially restored the epithelial tight-junction proteins and reduced plasma endotoxin and markers of oxidative stress and inflammation in CKD rats.157 In another study, AST-120 decreased serum levels of indoxyl sulfate and slowed the progression of CKD by reducing the profibrotic gene expression in the rat remnant kidney.158 In patients with CKD, administration of AST-120 significantly decreased the serum and urine levels of indoxyl sulfate and improved the slope of the 1/serum creatinine-time plot.159,160 AST-120 treatment of patients with CKD has also delayed the time to dialysis initiation.161

**Miscellaneous**

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are lipid-lowering drugs with anti-inflammatory properties.162 Abe et al.163 demonstrated that statins partially attenuated the development of adipose tissue inflammation in obese mice, which might be associated with an inhibitory effect of statins on TLR4-triggered expression of IFN-β via MyD88-independent signaling pathway in macrophages. Atorvastatin is known to affect LPS indirectly by causing impaired TLR4 recruitment into the lipid raft, thereby affecting anti-inflammatory responses.164 In a small study, optimized BP control with antihypertensive agents decreases endotoxin levels.165 The mechanism of this beneficial effect is unknown.

**CONCLUSIONS AND FUTURE DIRECTIONS**

Resident microbiota outnumber the human host cells by 10-fold, with metabolic activity in excess of that of the liver and a combined microbiome that is estimated to be 100 times greater than that of the human.166 In 2007, the Human Microbiome Project was established to characterize the human microbiome and analyze its role in health and disease.167 The project serves as a “roadmap” for discovering the roles these microorganisms play in human health and disease, with the goal of metagenomic characterization of microbial communities from 300 healthy individuals over time. Not long ago, the products of intestinal putrefaction were considered the primary uremic toxins. The recent explosion of knowledge on the metabolic potential of gut microbiome and its critical role in the pathogenesis of several chronic inflammatory diseases has led the nephrologist to refocus on the gut as a potential cause of CKD-related complication and a target organ for attenuating uremia-related complications. Therefore, it is time for more clinical and basic research studies to further our understanding of the role of the gut microbiome in progression of CKD and its associated complications. Finally, interventions aimed at establishing gut symbiosis and blocking microbiome-related pathogenic biochemical pathways should be explored in order to develop interventions to ameliorate uremic syndrome.

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**DISCLOSURES**

None.

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