

Chronic Kidney Disease: The Gut-Kidney Connection?

Jeffrey Bland, PhD, FACN, FACB, Associate Editor

Abstract

Among strategies for both the prevention and treatment of renal disease, reduction of uremic toxins and bacterial lipopolysaccharides that activates toll-like receptors and improvement in the composition of the microbiome represent valuable and clinically proven approaches. Dietary components—specifically soluble and insoluble prebiotic fibers; phytochemicals such as curcumin, berberine, epigallocatechin gallate, and withanolides that modulate gut immune function and improve

detoxification of uremic toxins; and supplemental, clinically tested probiotics—constitute a family of therapeutics that can positively affect patients. In addition, the bidirectional relationship of the microbiome to kidney disease is an important concept in designing a personalized approach to the management of kidney disease, especially with regard to its relationship to cardiovascular disease.

*Jeffrey Bland, PhD, FACN, FACB, is the president and founder of the Personalized Lifestyle Medicine Institute in Seattle, Washington. He has been an internationally recognized leader in nutrition medicine for more than 25 years. Dr Bland is the cofounder of the Institute for Functional Medicine (IFM) and is chairman emeritus of IFM's Board of Directors. He is the author of the 2014 book *The Disease Delusion: Conquering the Causes of Chronic Illness for a Healthier, Longer, and Happier Life*.*

In life, our experiences inform our thinking and often guide us to new perspectives on topics we thought we fully understood. In a column I published last winter—“Kidney Disease: Personalized Lifestyle Medicine Makes a Difference¹”—I recounted a story about a chance conversation that led me to pursue a greater understanding of the role of personalized lifestyle medicine in the prevention and treatment of kidney disease. My focus in that article was to discuss the prevalence of kidney disease and its economic burden. I cited studies on the role of insulin resistance, hypertension, smoking, excessive alcohol consumption, and diets high in sugar and saturated fats.¹ After compiling my research, I came to the conclusion that although no current therapy can successfully cure chronic kidney disease (CKD), the application of personalized lifestyle medicine may prove to be the most effective solution for improving outcomes in patients with this serious condition.

When I wrote that article on kidney disease, I did not anticipate that a follow-up—a “part 2,” if you will—was close at hand. But, as the great scientist Dr Louis Pasteur

was quoted as saying, “Chance favors the prepared mind.” Just a few weeks after the article was published, I was approached by an individual—a dedicated registered dietitian and clinical nutritionist—who asked an intriguing question: Do autoimmune diseases of the kidney have a relationship to the intestinal microbiome? For me, the question brought back memories from my years at the Functional Medicine Research Center, where we had seen patients with lupus nephritis and antibody-induced glomerulonephritis. Some of these patients had responded positively to a personalized lifestyle/functional medicine treatment plan that included a gastrointestinal restoration component that we referred to, at that time, as the 4R Program. The 4R Program involved removal of antigens and infectious organisms from exposure to the gut, replacement of digestive enzymes and stomach acid as needed, reinoculation of the gut with symbiotic microflora using prebiotics and probiotics, and supporting the repair of the intestinal mucosal lining with nutrients such as glutamine, glycine, zinc, pantothenic acid, and omega-3 fatty acids.

My colleague, the nutritionist, was trying to find a way to help pediatric patients with autoimmune nephritis, and so I made a commitment to dig deeper into the gut/kidney connection. Now several months into this effort, my exploration of this subject has not only involved discussions with several prominent nephrologists and a review of recent studies, but also some time spent revisiting my own early work involving the development of medical nutrition education programs. It was during this period of my career—now some 35 years ago—that I often lectured on the topic of indoxyl sulfate, also known as indican.

Endogenous Toxins in Kidney Diseases

Kidney diseases are complicated and multifactorial. A complete understanding of the mechanisms that underlie the pathogenesis of these conditions remains unclear. With that said, however, strong evidence suggests that both toxins and inflammatory immune factors play a significant etiological role regardless of the specific type of kidney disease.²

Uremic toxins are derived from the intestinal metabolism of partially digested protein by specific species within the microbiome, and these are well known to promote CKD.^{3,4} These enteric toxins include protein bacterial metabolites such as indoleamines, urea, and indoxyl sulfate produced by the microbiome, which influence health through the gut-kidney axis. It has been shown that indoxyl sulfate, a bacterial breakdown product of the amino acid tryptophan in dietary protein, is an independent risk factor for both kidney disease and heart disease.⁵ Work in the past few years has clearly demonstrated that dysbiosis of the intestinal microbiome contributes to the progression of CKD.^{6,7} It is also recognized that dysbiosis is associated with increased intestinal permeability (or “leaky gut”), which amplifies the absorption of enteric toxins and further contributes to CKD.⁸ Based on findings such as these, it appears likely that the absorption of certain endotoxins can induce the production of antibodies, including some that could be cross reactive with the kidney and, therefore, may contribute to the development of glomerulonephritis.

My early work in this area—which I referred to at the start of this article—began in 1976, when I was the director of the Bellevue Redmond Medical Laboratory in Seattle, Washington. My team and I developed the urinary indican test for indoxyl sulfate as a surrogate marker for intestinal dysbiosis and endotoxicity. During the years I spent managing the lab, we analyzed the results of thousands of patients and found that individuals with elevated levels of urinary indoxyl sulfate correlated with chronic health problems, including alterations in liver function, fatigue, and mood disorders. Although this work took place decades before the role of the microbiome composition on urinary indoxyl sulfate excretion was understood, we recognized there was a significant relationship among the diet, gut bacteria, and chronic health issues.

Naturally, I have continued to follow the research on indoxyl sulfate throughout my career. It has recently been reported that serum indoxyl sulfate levels predicts both renal function deterioration⁹ and cognitive impairment in early-stage CKD.¹⁰ It is a candidate target for the prevention and treatment of CKD, and its relationship to cardiovascular disease risk is also a key area of research.¹¹ Indoxyl sulfate appears to be the uremic toxin that links hemostatic system disturbances with the prevalence of cardiovascular disease in patients with CKD.¹² In essence, indoxyl sulfate can be considered a nephro-vascular endotoxin.¹³

The inverse relationship between the ratio of dietary fiber to protein levels in the diet to the indoxyl sulfate has been reported in a recent study.¹⁴ In this study, 40 patients with CKD had their dietary fiber and protein intake evaluated and their serum indoxyl sulfate measured. It was determined that increasing the dietary fiber to dietary protein ratio resulted in a reduction in indoxyl sulfate. This suggests that a diet that is adequate in prebiotic dietary fiber is important in maintaining a microbiome that produces less uremic toxins.

Inflammatory Mediators, Autoimmunity and Kidney Disease

Antineutrophil cytoplasmic antibody associated vasculitis (AAV) comprises a group of autoimmune disorders that are associated with inflammatory kidney disease.¹⁵ The source of this autoimmune inflammatory process has been a subject of research for some time. It is known that prophylactic antibiotic therapy prevents relapses of this condition in those people who have had this diagnosis, suggesting a close link between infection and AAV. It is also known that bacterial infection initiates a complex immune response including activation of the innate immune system through the toll-like receptor family. Toll-like receptors are part of the signaling network in the innate immune system, which regulates immune response to bacterial infection. Recent evidence implicates activation of toll-like receptors in the initiation of inflammation that is associated with various kidney disorders.¹⁵ There are more than 11 members of the toll-like receptor family, including toll-like receptor 4 (TLR-4), which is activated by lipopolysaccharides (LPS) that are released from the cell walls of specific gram negative bacteria. Within the gut associated immune system, specific microbial bacteria release LPS, which triggers TLR-4 activation and the subsequent release of inflammatory cytokines, such as tumor necrosis factor α . TLR-4 activation has been identified to be critically involved in immune responses of AAV. In animal studies, it has been demonstrated that LPS amplifies antimyeloperoxidase antibody-induced glomerulonephritis in a TLR-4 dependent manner.¹⁶ It is well known that TLRs are expressed not only on the kidney, but also in cells in the intestinal tract, systemic immune system, and brain.

The link between toll-like receptors and kidney disease has been further substantiated with the identification of signaling pathways that play a role in communication between the intestinal microbiome and the kidneys.¹⁷ Research of this nature establishes the gut-kidney connection extends beyond a focus on uremic toxins.

A connection between activation of the toll-like receptors and kidney disease associated with autoimmune systemic lupus erythematosus (SLE) has also been established.¹⁸ As a result, it is now recognized that toll-like receptors represent a potential drug target for the treatment of kidney injury associated with SLE.¹⁹ Evidence suggests that specific genetic polymorphisms of the toll-like

receptor family increase the risk to SLE and autoimmune disease of the kidney owing to an amplified sensitivity to bacterial LPS produced by species of bacteria within the intestinal microbiome.²⁰

Potential Approaches to Managing the Gut-Kidney Association With Disease

It is now well established that the gut microbiome is altered in kidney disease and that the resultant dysbiosis contributes to the progression of CKD.²¹ Recent studies have demonstrated that interventions that improve the composition of the microbiome can reduce both uremic toxins and inflammatory immune activity in patients with kidney disease.²² The oral administration of agents that absorb intestinal toxins, and synbiotics that improve the composition of the microbiome, both result in improved kidney function in people with CKD.²³

Certain phytochemicals found in specific foods have demonstrated beneficial effects on the microbiome. Emodin, a naturally occurring anthraquinone present in the roots and bark of numerous plants including *Aloe vera* and the Chinese herb rhubarb (*Da Huang*), has been demonstrated to reduce uremic toxins and has been used in China for centuries for the treatment of CKD.²⁴ A study in Asia to test the potential medical applications of *Da Huang* employed an enema of a decoction of the herb in rats with CKD. This treatment was found to both improve the composition of the microbiome and reduce endotoxins, including urea and indoxyl sulfate. The most significant alteration in the microbiome was a reduction in *Clostridium* spp and an increase in the beneficial bacteria *Lactobacillus* spp.²⁵

Among strategies for both the prevention and treatment of renal disease, reduction of uremic toxins and bacterial LPS that activates toll-like receptors and improvement in the composition of the microbiome represent valuable and clinically proven approaches. Dietary components—specifically soluble and insoluble prebiotic fibers; phytochemicals such as curcumin,²⁶ berberine,²⁷ epigallocatechin gallate,²⁸ and withanolides²⁹ that modulate gut immune function and improve detoxification of uremic toxins; and supplemental, clinically tested probiotics—constitute a family of therapeutics that can positively affect patients.^{30,31} In addition, the bidirectional relationship of the microbiome to kidney disease is an important concept in designing a personalized approach to the management of kidney disease, especially with regard to its relationship to cardiovascular disease.

References

- Bland JS. Kidney disease: Personalized lifestyle health care makes a big difference. *Integr Med (Encinitas)*. 2016;15(6):14-16.
- McIntyre CW, Harrison LE, Eldehni MT, et al. Circulating endotoxemia: A novel factor in systemic inflammation and cardiovascular disease in chronic kidney disease. *Clin J Am Soc Nephrol*. 2011;6(1):133-141.
- Ramezani A, Raj DS. The gut microbiome, kidney disease, and targeted interventions. *J Am Soc Nephrol*. 2014;25(4):657-670.

- Soulage CO, Koppe L, Fouque D. Protein-bound uremic toxins...new targets to prevent insulin resistance and dysmetabolism in patients with chronic kidney disease. *J Ren Nutr*. 2013;2(6):464-466.
- Wing MR, Patel SS, Ramezani A, Raj DS. Gut microbiome in chronic kidney disease. *Exp Physiol*. 2016;101(4):471-477.
- Tremaroli V, Backhed F. Functional interactions between the gut microbiota and host metabolism. *Nature*. 2012;489(7415):242-249.
- 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(6):587-592.
- Anders HJ, Andersen K, Stecher B. The intestinal microbiota, a leaky gut, and abnormal immunity in kidney disease. *Kidney Int*. 2013;(6):1010-1016.
- Briskey D, Tucker P, Johnson DW, Coombes JS. The role of the gastrointestinal tract and microbiota on uremic toxins and chronic kidney disease development. *Clin Exp Nephrol*. 2017;21(1):7-15.
- Yeh YC, Huang MF, Liang SS, et al. Indoxyl sulfate, not p-cresyl sulfate, is associated with cognitive impairment in early-stage chronic kidney disease. *Neurotoxicology*. 2016;53:148-152.
- Mafra D, Lobo JC, Barros AF, Koppe L, Vaziri ND, Fouque D. Role of altered intestinal microbiota in systemic inflammation and cardiovascular disease in chronic kidney disease. *Future Microbiol*. 2014;9(3):399-410.
- Kaminski TW, Pawlak K, Karbowska M, Mysliwiec M, Pawlak D. Indoxyl sulfate – the uremic toxin linking hemostatic system disturbances with the prevalence of cardiovascular disease in patients with chronic kidney disease. *BMC Nephrol*. 2017;18(1):35.
- Niwa T. Indoxyl sulfate is a nephro-vascular toxin. *J Ren Nutr*. 2010;20(suppl 5):S2-S6.
- Rossi M, Johnson DW, Xu H, et al. Dietary protein-fiber ratio associates with circulating levels of indoxyl sulfate and p-cresyl sulfate in chronic kidney disease patients. *Nutr Metab Cardiovasc Dis*. 2015;25(9):860-865.
- Wang H, Gou SJ, Zhao MH, Chen M. The expression of Toll-like receptors 2, 4 and 9 in kidneys of patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis. *Clin Exp Immunol*. 2014;177(3):603-610.
- Shirali AC, Goldstein DR. Tracking the toll of kidney disease. *J Am Soc Nephrol*. 2008;19(8):1444-1450.
- Li M, Zhou Y, Feng G, Su SB. The critical role of Toll-like receptor signaling pathways in the induction and progression of autoimmune diseases. *Curr Mol Med*. 2009;9(3):365-374.
- Marshak-Rothstein A. Toll-like receptors in systemic autoimmune disease. *Nat Rev Immunol*. 2006;6(11):823-835.
- Wagner H. Endogenous TLR ligands and autoimmunity. *Adv Immunol*. 2006;91:159-173.
- Anders HJ, Banas B, Schlondorff D. Signaling danger: Toll-like receptors and their potential roles in kidney disease. *J Am Soc Nephrol*. 2004;15(4):854-867.
- Sabatino A, Regolisti G, Brusasco I, Cabassi A, Morabito S, Fiaccadori E. Alterations of intestinal barrier and microbiota in chronic kidney disease. *Nephrol Dial Transplant*. 2015;30(6):924-933.
- Rossi M, Johnson DW, Campbell KL. The kidney-gut axis: Implications for nutrition care. *J Ren Nutr*. 2015;25(5):399-403.
- Cigarran Guldris S, Gonzalez Parra E, Cases Amenos A. Gut microbiota in chronic kidney disease. *Nefrologia*. 2017;7(1):9-19.
- Li Y, Xiong W, Yang J, et al. Attenuation of inflammation by emodin in lipopolysaccharide-induced acute kidney injury via inhibition of toll-like receptor 2 signal pathway. *Iran J Kidney Dis*. 2015;9(3):202-208.
- Zeng YQ, Dai Z, Lu F, et al. Emodin via colonic irrigation modulates gut microbiota and reduces uremic toxins in rats with chronic kidney disease. *Oncotarget*. 2016;7(14):17468-17478.
- Soetikno V, Sari FR, Lakshmanan AP, et al. Curcumin alleviates oxidative stress, inflammation, and renal fibrosis in remnant kidney through the Nr1h2-keap1 pathway. *Mol Nutr Food Res*. 2013;57(9):1649-1659.
- Guo Z, Sun H, Zhang H, Zhang Y. Anti-hypertensive and renoprotective effects of berberine in spontaneously hypertensive rats. *Clin Exp Hypertens*. 2015;37(4):332-339.
- Delwing-Dal Magro D, Roecker R, et al. Protective effect of green tea extract against proline-induced oxidative damage in the rat kidney. *Biomed Pharmacother*. 2016;83:1422-1427.
- Minhas U, Minz R, Das P, Bhatnagar A. Therapeutic effect of *Withania somnifera* on pristane-induced model of SLE. *Immunopharmacology*. 2012;20(4):195-205.
- Koppe L, Mafra D, Fouque D. Probiotics and chronic kidney disease. *Kidney Int*. 2015;88(5):958-966.
- Yacoub R, Kaji D, Patel SN, et al. Association between probiotic and yogurt consumption and kidney disease: Insights from NHANES. *Nutr J*. January 2016;15:10.