Altered Microbiome in Chronic Kidney Disease

Reviewed by:

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Introduction

Chronic kidney disease (CKD), a debilitating condition, results in systemic inflammation and oxidative stress. This leads to progression of kidney disease and the associated complications including cardiovascular disease, cachexia, and anemia. The gastrointestinal tract is recognized as a major source of this systemic inflammation and oxidative stress as the intestinal microbiome is markedly altered in CKD (Table 1). Altered microbiome results in increased production of bacteria-derived uremic toxins such as indoxyl sulphate, p-cresyl sulphate, and trimethylamine-N-oxide (TMAO). Role for gut-derived uremic toxins has been established in varied studies in promoting multiorgan dysfunction (Figure 1) via inflammatory, oxidative stress, and apoptosis pathways. Indoxyl sulfate and p-cresyl sulfate are well characterized uremic toxins that induce inflammation and leukocyte activation and have been associated with increased systemic inflammation and mortality in CKD patients. TMAO is a toxin generated by conversion of choline to trimethylamine by the gut microbial flora. Elevated levels of TMAO have been linked to increased 5-years mortality risk in CKD subjects after multivariate adjustment. Levels of circulating endotoxin, increase with severity of CKD stage and are most elevated in end-stage renal disease (ESRD) patients on maintenance dialysis.[1,2]

Relationship Between the Altered Microbiome and Systemic Inflammation in CKD

The symbiotic intestinal microbiome plays an integral role in the host's health. A healthy microbiome is defined by the diversity in microbial species that provide a varied repertoire of metabolic functions. Alterations in gut microbiota and a myriad of host responses have been implicated in progression of CKD, increased cardiovascular risk, uremic toxicity and inflammation. Mounting evidence suggest that changes in the biochemical environment of the gut in CKD affect the integrity of intestinal epithelial barrier and the composition and function of the microbiome.3 Bacterial-derived fragments and uremic toxins enter the bloodstream through the leaky gut. The adverse effects of the toxic byproducts by dysbiotic microbiota are compounded by the reduction of numerous useful micronutrients made by the normal microbiota. This contributes to chronic local and systemic inflammation which further promotes disruption

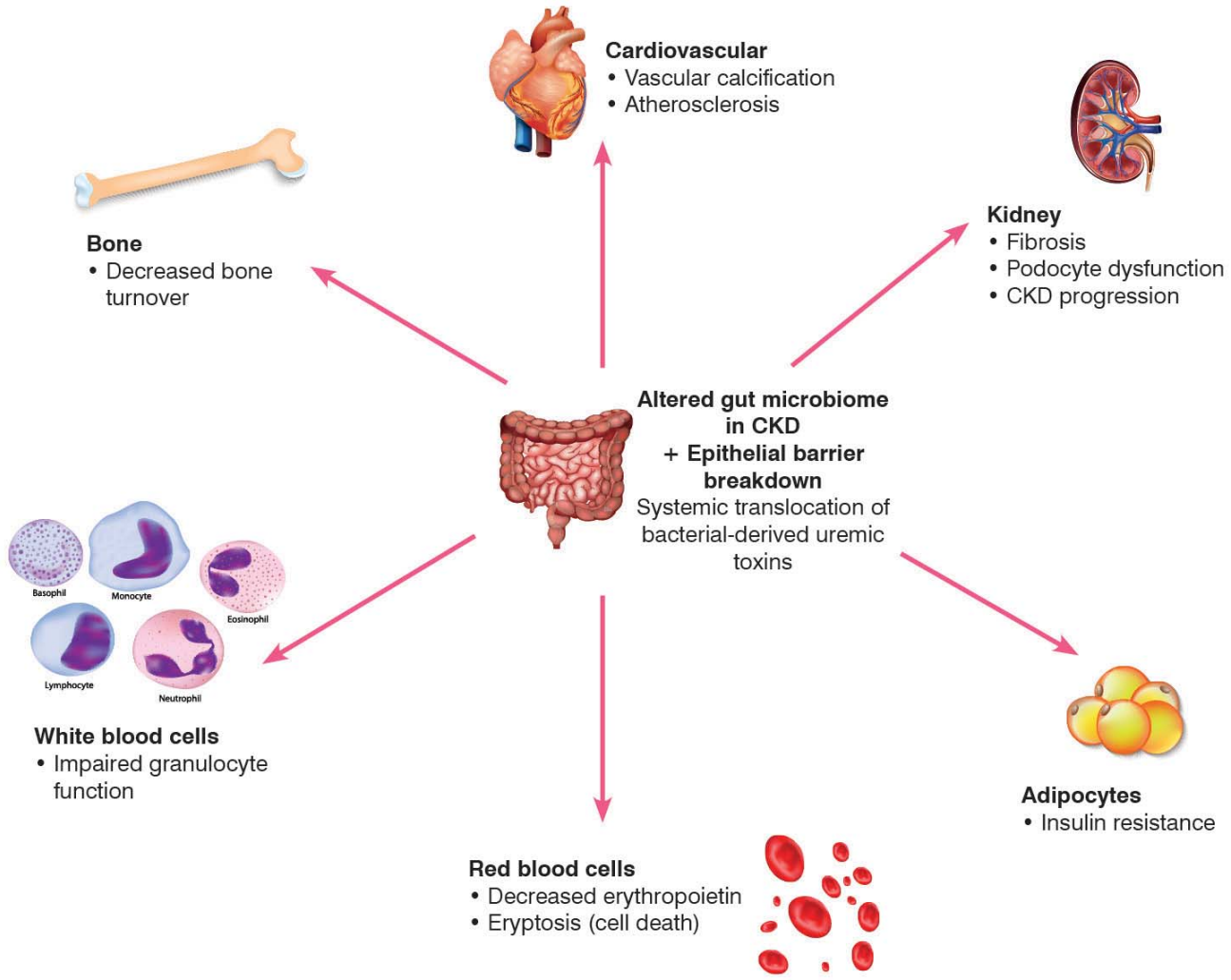
Table 1: Gut microbiota changes in CKD

Intestinal tract	Normal	CKD/ACKD
Stomach	*Lactobacillus* *Helicobacter*	No change
Duodenum	*Staphylococcus* *Streptococcus* *Lactococcus*	Increased
Jejunum	*Enterococcus* *Streptococcus* *Lactobacillus*	Increased
Ileum	*Enterobacteriaceae* *Bacteroides* *Clostridium* Bacterial fragments	Increased
Colon	Firmicutes *Bacteroides* Actinobacteria Proteus *Clostridium* *Lactobacilli* *Prevotellaceae*	**Increased:** Proteobacteria, Enterobacteria, *E. coli*, Acinetobacter, *Proteus spp.* **Decreased:** *Lactobacillus, Bifidobacterium* spp.
	Fusobacterium	Aerobic overgrowth of at least 100 times
	TM7	Increase of *Clostridium perfringens*

Abbreviations: CKD, chronic kidney disease; ACKD, advanced chronic kidney disease.

Adapted from: Cigarran Guldris S, González Parra E, Cases Amenós A. Gut microbiota in chronic kidney disease. [Article in English, Spanish] *Nefrologia.* 2017;37(1):9-19.

Figure 1: Role of gut-derived uremic toxins in promoting multiorgan dysfunction



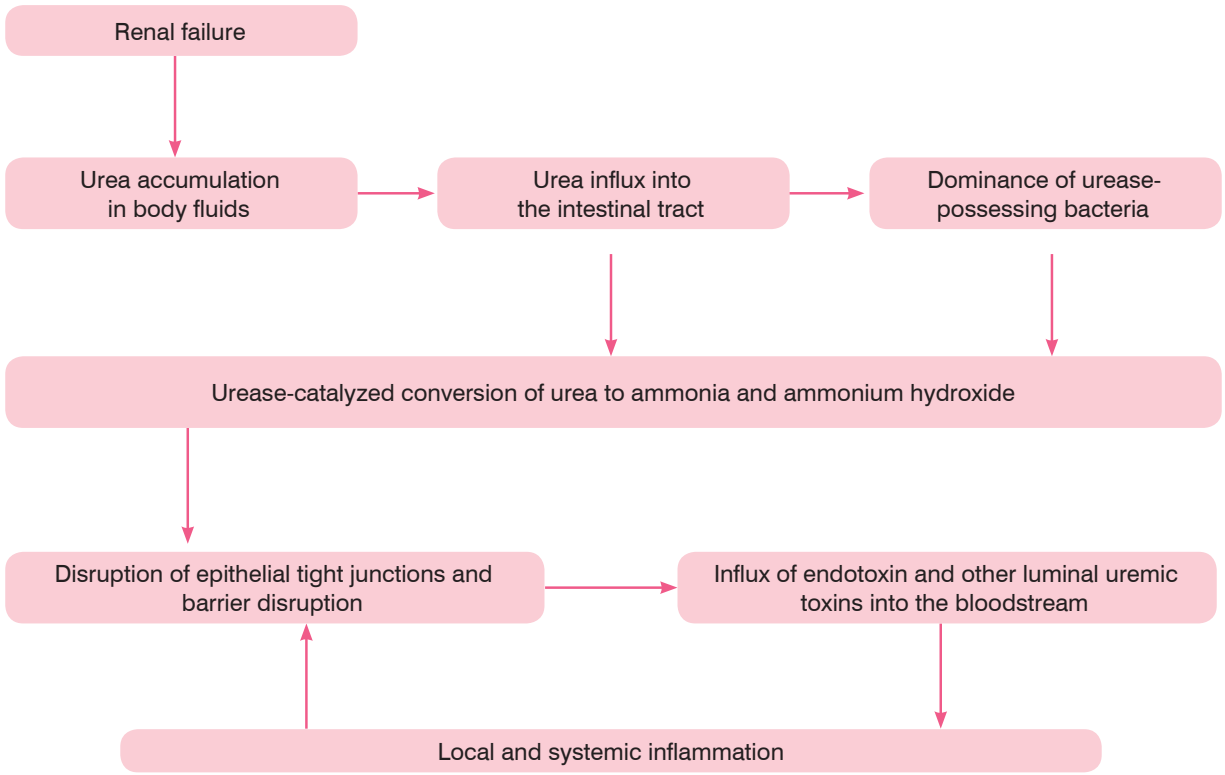
Adapted from: Lau WL, Savoj J, Nakata MB, Vaziri ND. Altered microbiome in chronic kidney disease: systemic effects of gut-derived uremic toxins. *Clin Sci (Lond).* 2018;132(5):509-22.

of the gut epithelial barrier, thus forming a vicious cycle that impacts progression of renal failure and its associated adverse outcomes. The underlying mechanisms of the uremia-induced gut microbial dysbiosis, disruption of the intestinal epithelial barrier, and their contribution to systemic inflammation in CKD are summarized in Figure 2.[1]

Gut Ecosystem in CKD and Immunity

The intestinal microbiota evolves as an important element in the regulation of immune system. It is likely that uremia, an illness that accompanies kidney failure and chronic kidney disease, directly or indirectly affect the composition of the intestinal microbiota as well as the intestinal barrier. An increased translocation of bacterial products across the intestinal barrier will activate innate immunity, which could provide an explanation for the systemic inflammation and immunodeficiency that is associated with CKD and ESRD.[4] Persistent systemic inflammation contributes to atherogenesis, cardiovascular disease, anemia, cachexia, and bone loss, whereas acquired immunodeficiency leads to impaired response to vaccination and to microbial infections. This, in turn, increases the frequency and severity of microbial infections which further contributes to activate innate immunity and systemic inflammation.[5] Persistent innate immune activation involves the induction of immunoregulatory mediators that suppress innate and adaptive immunity, similar to the concept of endotoxin tolerance or immune paralysis in advanced sepsis or

Figure 2: Underlying mechanisms of altered microbiome and systemic inflammation in CKD



Adapted from: Lau WL, Vaziri ND. The Leaky Gut and Altered Microbiome in Chronic Kidney Disease. *J Ren Nutr.* 2017;27(6):458-61.

chronic infections (Figure 3). This results in the clinical syndrome of persistent inflammation accompanied by an immunosuppressive state. Together, these immunological disorders have a strong negative impact on the survival of CKD patients.[4]

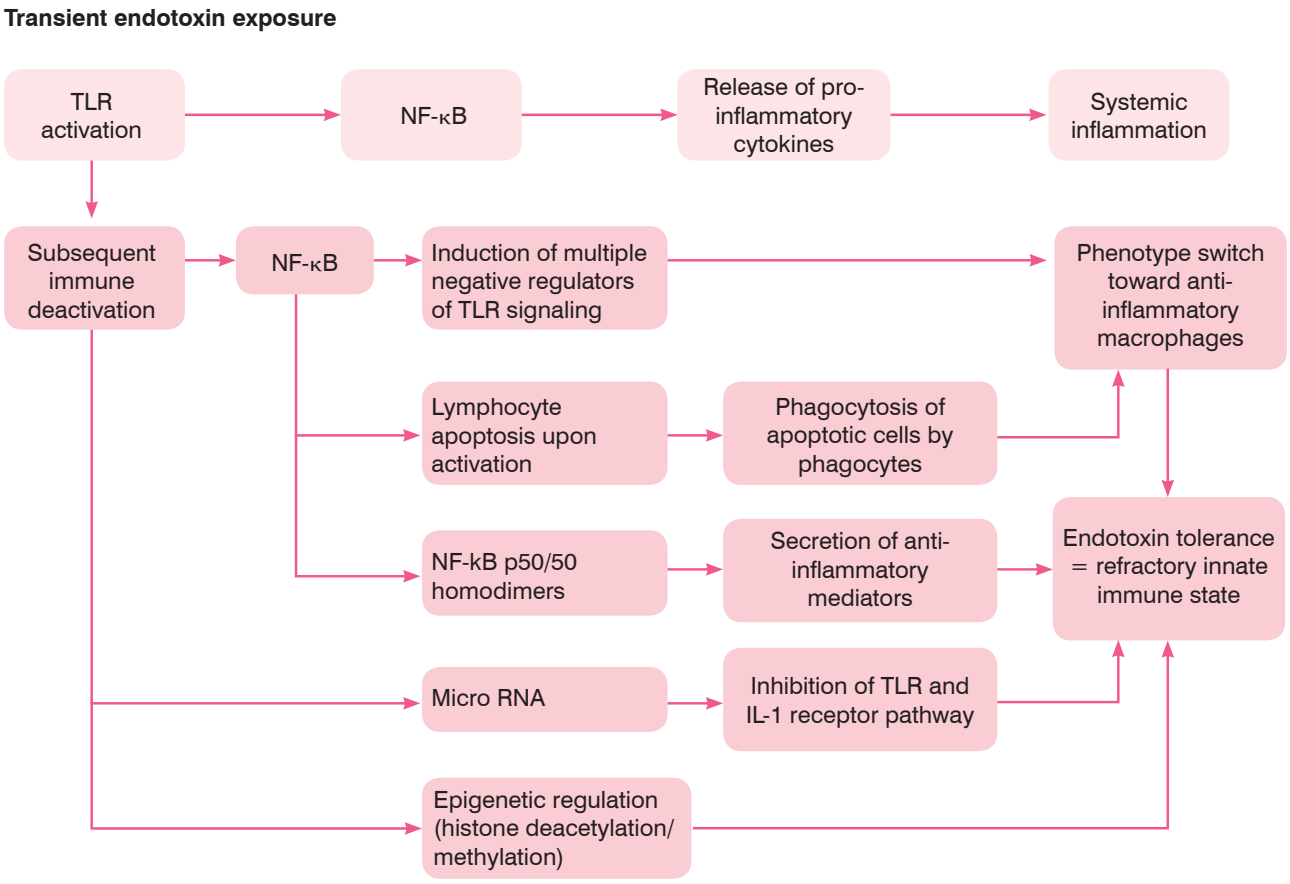
Interventions to Attenuate Gut Microbiome Disturbances in CKD

In CKD, nutritional management and supplementation, including salt and protein restriction, vegetable intake, and the use of pro-, pre- and synbiotics, has a variety of potential benefits.[6] Interventions intended to lower uremic toxin production includes restricting intake of uremic toxin precursors (lower protein intake), by restoring a more balanced gut microbiome (food supplements), and by interventions aiming to enhance the disposal of these toxins (adsorptive therapies).[7]

Dietary management and supplementation with prebiotics, probiotics, and synbiotics have been highlighted in this scenario. This approach focuses on the modulation of the carbohydrate/protein ratio delivered into the colon and/or on the composition and metabolism of microbiota. The prescription of a low-protein diet is an approach widely employed for non-dialysis dependent-CKD patients to control metabolic disturbances and uremic symptoms and to slow the progression of the disease. Dietary protein restriction limits the influx of urea into the gut and potentially contributes to prevent harmful changes in the gut ecosystem.[5] Furthermore, adsorbent therapies such as AST-120, reduces uremic toxins in patients with CKD. It is an orally ingested intestinal spherical carbon adsorbent which adsorbs indole. Indole, the precursor of indoxyl sulfate, is derived from the metabolism of tryptophan by bacteria within the gastrointestinal tract. Therefore, adsorbent therapy is used to attenuate indoxyl sulfate accumulation in patients with CKD.[7]

Overall improvement in the health status of individual with CKD entails decreased circulating levels of blood urea nitrogen and uric acid, reduction of inflammation and oxidative stress, amelioration of bowel transit, glucose and lipid metabolism, acid-base balance and hypertension.[6]

Figure 3: Leaky gut induces systemic immune-suppression in CKD patients



Abbreviations: TLR: toll-like receptors; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; RNA: ribonucleic acid; IL-1: interleukin 1

Adapted from: Anders HJ, Andersen K, Stecher B. The intestinal microbiota, a leaky gut, and abnormal immunity in kidney disease. *Kidney Int.* 2013;83(6):1010-6.

Conclusion

The gut environment is altered in CKD due to the restrictive diet and influx of urea from the circulation, favoring a microbial population that generates uremic toxins including indoxyl sulphate, p-cresyl sulphate, TMAO, indole-3 acetic acid, and phenylacetylglutamine. Intestinal inflammation and breakdown of the epithelial barrier promote systemic translocation of these bacterial by-products with widespread oxidative stress damage to the cardiovascular, kidney, erythropoiesis, bone-mineral, and endocrine systems. Strategies to reverse microbiome dysbiosis are a novel therapeutic target. Small randomized clinical trials using pre- and probiotics have shown some benefit in terms of decreasing circulating levels of uremic toxins and improving quality of life, but larger trials are needed to examine impact on cardiovascular or kidney morbidity.

References

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