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## The Chronic Kidney Disease—Colonic Axis

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### ABSTRACT

Chronic kidney disease (CKD) has long been known to cause significant gastrointestinal and colonic pathology. Recent advances in understanding of the role of colonic bacterial microbiome and its function and composition in health and disease have revealed previously unappreciated effects of CKD-associated colonic pathology on the development of uremic complications. CKD can result in profound changes in the microbiome composition and biosynthetic pattern, and the structure and function of the colon. Increases in bacteria that produce urease, uricase, p-cresol- and indole-forming enzymes and the depletion of bacteria that possess short chain fatty acid forming enzymes have been described in human and animal models. Disruption of the colonic epithelial tight

junction in different animal models of CKD has been reported and is largely due to the conversion of luminal urea to ammonia by urease possessing bacteria. Together, these changes contribute to the pathogenesis of systemic inflammation and uremic toxicity by allowing the translocation of endotoxin and microbial fragments into the circulation. Additionally, colonic bacteria are the main source of several well-known pro-inflammatory uremic toxins such as indoxyl sulfate, P-cresol sulfate. This review is intended to provide an overview of the effects of CKD on the colonic microbiome and the intestinal epithelial barrier structure and function and their role in the pathogenesis the systemic inflammation and uremic toxicity.

Chronic kidney disease (CKD) has long been known to cause significant gastrointestinal and colonic pathology, including bowel inflammation, ulcerations and necrosis (1). The recent explosion of knowledge surrounding the role of the colon and its bacterial flora (microbiome) in health and disease has revealed the previously unappreciated effect of CKD-associated colonic pathology on the development of uremic complications. It is becoming evident that CKD-associated pathologic changes on the colonic mucosa and microbiome result in translocation of bacteria, bacterial products and uremic toxins into the systemic circulation. These pro-inflammatory events contribute to the chronic inflammation and oxidative stress associated with CKD and its many complications (2–5). In this article we will review the effects of CKD-associated changes in the structure and function of the colonic epithelial barrier and the composition of the fecal microbiome.

### The Normal Colon and Microbiome

The colon contains over  $10^{12}$  microbes/ml which account for over 65% of the weight of the fecal material (6). These bacteria provide the host with a variety of benefits including protection against pathogenic bacteria, production of short chain fatty acids that provide a critical source of nutrition to enterocytes, digestion of complex carbohydrates, production of various vitamins such as group B vitamins and vitamin K, and synthesis of amino acids (7–12). In addition, the intestinal microbiome plays a major part in shaping the immune system (13,14).

Advances in genetic sequencing and increased research funding have resulted in increased characterization of the human microbiome. A healthy microbiome is defined by a large number of different bacterial species that can provide a wide variety of metabolic functions (15). However, despite the large variety of bacterial species observed, there is remarkable commonality. Over 50% of healthy individuals share the same 75 bacterial species and over 90% of the bacteria found in the colon belong to the Bacteroidetes and Firmicutes phyla (16). Humans can be divided into three different bacterial enterotypes that are defined by the abundance of bacteria from different genus, i.e., Bacteroides, Prevotella or Ruminococcus, and possess a different biosynthetic pattern (17). Bacteria that synthesize

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biotin and riboflavin are represented to a greater degree in Enterotype 1 while thiamine and folate producing bacteria are enriched in enterotype 2 (18). Although not clearly established, different enterotypes may be associated with obesity linked co-morbidities, cardiovascular disease and colonic cancer (17). The colonic mucosa functions as the body's barrier against these bacteria and their resultant products. This colonic mucosa is composed of epithelial enterocytes joined by an inter-cellular junctional complex. The enterocytes allow for the passive and active transport of solutes and water and the junctional complex serves as the barrier against the colonic luminal contents (19). The normal microbiome is necessary for the maintenance of healthy colonic mucosa. Colonic epithelial cells derive 60% of their energy from bacterial fermentation products. These short-chain fatty acids also serve as normal modulators of enterocyte growth and maturation (20).

### The CKD-Colonic Axis

CKD can result in significant alteration in the colonic microbiome (dysbiosis), and in the structure and function of the colonic mucosa. These changes in turn, contribute to the pathogenesis and possibly to the progression of CKD.

In CKD urea influx into the colon is increased and converted to ammonia by bacteria possessing urease. The ammonia is then converted to ammonium hydroxide which can raise the colonic pH and result in mucosal damage (1,21). Intestinal secretion of uric acid and oxalate also increase in CKD (22–24) and provide alternative substrates for bacteria that normally digest complex carbohydrates. The reduced intake in CKD of high-fiber, potassium-rich fruit and vegetables causes changes in microbiome composition and function. Finally, the frequent use of various drugs such as antibiotics which result in well recognized alterations of the gut bacterial composition and large consumption of various phosphate binders likely add to the presence of dysbiosis.

A recent study has confirmed the hypothesized CKD-associated dysbiosis in patients with end-stage renal disease (ESRD) (25). Using bacterial DNA isolated from fecal samples, these investigators showed highly significant differences in the abundance of over 200 bacterial operational taxonomic units (OTUs are used to classify species or groups of bacteria using DNA sequence data) between hemodialysis patients and the healthy control groups. These findings were confirmed in rats with surgically-induced CKD. Compared to the control animals, the CKD rats showed significant differences in the abundance of 175 bacterial OTUs, (25). Additional studies by the same group, demonstrated that patients with ESRD had increased number of bacteria that possess urease, uricase, p-cresol- and indole-forming enzymes, and reduced number of bacteria that possess short chain fatty

acid forming enzymes (26). This CKD-induced dysbiosis can result in increased production toxic, pro-inflammatory uremic substances.

This assumption was confirmed by Aronov et al. who verified the colonic origin of uremic compounds in the plasma of ESRD patients by comparing data from those who had required colectomy with those with an intact colon (27). They identified over 30 plasma compounds, including indoxyl sulfate, p-cresol sulfate, in hemodialysis patients with colons that were either absent or found in lower concentrations in patients with colectomies, thus proving that the colon is the main source of many uremic solutes.

CKD-associated changes can result in the alteration of the colonic mucosa and allow for the leaking of bacterial products and toxins into the systemic circulation. Indirect evidence of this effect has been found in several studies of animals or patients with CKD. These studies have shown the presence of endotoxemia in the absence of clinical infection, (28–32), increased intestinal permeability to high molecular weight polyethylene glycols (33,34), presence of bacteria in the intestinal wall, and mesenteric lymph nodes of CKD rats (35) and the presence of the gut derived microbial DNA in the blood of hemodialysis-treated and nondialyzed CKD patients (32,35–39). This disruption in the integrity of the colon can be due to a variety of pathogenetic events. Histologic evidence of chronic inflammation of the colon has been observed in hemodialysis patients (1) and animal models of CKD (40). Additionally, marked reduction of the tight junction proteins, claudin-1, occludin, and ZO1 has been described in the gut mucosa of CKD animals (40,41), likely due to the effects of uremic toxins, particularly urea. Vaziri et al., have shown that disruption of the tight junctions is in part mediated by the conversion of gut urea by bacterial urease to ammonia and ultimately ammonium hydroxide, a caustic compound capable of dissolving proteins (42,43). Other factors, such as edema of the intestinal wall and gut ischemia from excessive use of diuretics and hemodialysis associated hypotension can also result in impaired epithelial barrier (44–49).

Taken together, these observations provide compelling evidence that CKD results in impairment of the colonic microbiome and mucosal barrier function which results in translocation of bacteria, endotoxin and other toxins. These pathologic events cause local inflammation which in turn, causes depletion of tight junction proteins and hence further disruption of the barrier structure (Fig. 1). This phenomenon contributes to the systemic inflammation and oxidative stress that play a central role in CKD progression and its numerous complications (50).

### Therapeutic Interventions

These observations suggest several approaches that may prove effective in attenuating the CKD-

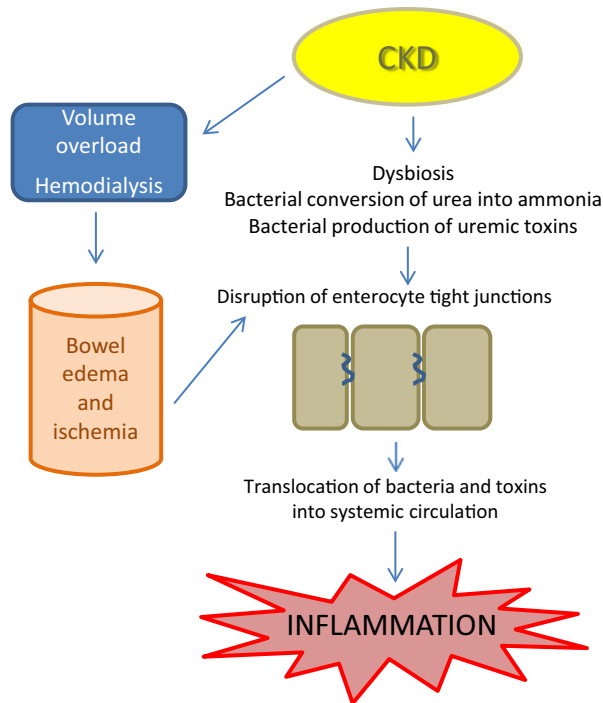


FIG. 1. Effect of CKD on the colonic microbiome (dysbiosis) and mucosal structure and function.

associated dysbiosis and colonic dysfunction and reduce inflammation and uremic toxicity.

Dietary interventions may improve the CKD-associated dysbiosis and intestinal barrier dysfunction (26,43,51). Use of restricted protein diets supplemented with keto analogs of amino acids has recently been shown to reduce levels of indoxyl sulfate (a colon-derived uremic toxin) in pre-dialysis patients with CKD (52). Increasing dietary fiber in CKD rats significantly improved intestinal epithelial tight junctions, reduced oxidative stress, inflammation, and resulted in less severe renal dysfunction (53). In a group of chronic hemodialysis patients, dietary fiber supplementation reduced serum concentration of indoxyl sulfate and p-cresol sulfate (54). Finally, improved dietary management of fluid and sodium intake may also turn out to be useful in ameliorating colonic-CKD pathology by minimizing the need for aggressive ultrafiltration and dialysis-associated hypo-perfusion of the bowel.

AST-120, the highly potent activated charcoal preparation, markedly reduced plasma concentration of gut-derived uremic toxins, indoxyl sulfate and p-cresol sulfate in CKD patients (55,56) as well as reducing oxidative stress, inflammation and the progression of CKD in animal models (57–60). Additionally, AST-120 attenuates the CKD-induced disruption of the gut epithelial tight junctions and reduces plasma endotoxin levels, and markers of oxidative stress and inflammation (61). Unfortunately, the recently completed randomized clinical trial of AST-120 in over 2000 patients failed to show any improvement in progression of CKD (62). This discrepancy in outcomes from previous AST-

120 trials (63,64) may have been due to inclusion of patients with slowly progressive CKD, poor adherence to the multiple doses of the study drug and possible regional differences in the timing of initiation of dialysis.

Attempts at improving the CKD-associated dysbiosis with the use of probiotics have also been rather disappointing. Several investigators have studied the effects of ingestion of various bacterial species (many with urease-possessing capabilities) on the systemic level of uremic toxins (65–70). Some have shown modest reductions in p-cresol (68–70) while others reported a marginal reduction in serum urea. In CKD patients, the randomized clinical trial of the probiotic Renadyl failed to reduce plasma concentration of protein bound uremic toxins, markers of systemic inflammation or quality of life parameters (67). This is not surprising since the CKD-associated alterations of colonic structure, function and microbiome composition are caused by a combination of changes that result in an unfavorable environment for the symbiotic microbiome. Thus, it is unlikely that simply providing the colon with more of the desired bacteria will restore their numbers unless it is accompanied with therapeutic interventions aimed at improving the altered biochemical environment. Prescribing urease-possessing bacteria to reduce serum urea level may be easier to achieve since the increased colonic influx of urea in CKD creates a hospitable environment for these bacteria. However, conversion of urea by these organisms to ammonia and ammonium hydroxide has been shown to be responsible for destruction of intestinal epithelial barrier. Thus, the use of some of these probiotic preparations may promote a leaky bowel, increase inflammation and cause harm.

## Conclusions

CKD results in profound changes in colonic structure and function, the integrity intestinal epithelial barrier structure and the composition of the fecal microbiome. These abnormalities lead to the generation and absorption of toxins which contribute to the systemic inflammation, uremic toxicity and contribute to the pathogenesis and possibly to the progression of CKD. Strategies aimed at lowering urea level, minimizing fluid overload, preventing bowel ischemic insults, as well as prescribing a high fiber diet, and the use of oral adsorbents may improve outcomes in this population.

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