Title
The Chronic Kidney Disease-Colonic Axis

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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 proinflammatory 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...
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 function of the colonic mucosa 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).

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 (out) (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

Therapeutic Interventions

These observations suggest several approaches that may prove effective in attenuating the CKD-
This discrepancy in outcomes from previous AST-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 the symbiotic microbiome. 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.

References