Title
The Chronic Kidney Disease-Colonic Axis

Permalink
https://escholarship.org/uc/item/5j94x3m3

Journal
Seminars in Dialysis, 28(5)

ISSN
0894-0959

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Publication Date
2015

DOI
10.1111/sdi.12381

Peer reviewed
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 of the systemic inflammation and uremic toxicity.

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
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 resul-
tant 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 nor-
mal microbiome is necessary for the maintenance of
healthy colonic mucosa. Colonic epithelial cells
derive 60% of their energy from bacterial fermenta-
tion 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 nor-
mally digest complex carbohydrates. The reduced
intake in CKD of high-fiber, potassium-rich fruit and
vegetables causes changes in microbiome composi-
tion and function. Finally, the frequent use of various
drugs such as antibiotics which result in well recog-
nized 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 abun-
dance 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 con-
trol 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, demon-
strated 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 dys-
biosis 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 com-
pounds in the plasma of ESRD patients by compar-
ing data from those who had required colectomy
with those with an intact colon (27). They identified
over 30 plasma compounds, including indoxyl sul-
фate, 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 alter-
ation 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 dis-
ruption of the tight junctions is in part mediated by
the conversion of gut urea by bacterial urease to
ammonia and ultimately ammonium hydroxide, a
causative compound capable of dissolving proteins
(42,43). Other factors, such as edema of the intesti-
nal 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 comp-
elling 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-
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.

References


