Gut microbiome in chronic kidney disease

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Overview
Normal gut microbiota influences the well-being of the host by contributing to its nutrition, metabolism, physiology, and immune function [1]. Disturbance of normal gut microbiota (dysbiosis) has been implicated in the pathogenesis of diverse illnesses such as obesity [2], type 2 diabetes [3], inflammatory bowel disease [4] and cardiovascular disease [5]. Quantitative and qualitative alterations in gut microbiota are noted in patients with CKD and ESRD [6].

Factors that modulate the gut microbiome
The gut microbiome is relatively stable, but adapts dynamically to changing environment and health. De Filippo and colleagues investigated the long-term effect of dietary pattern by comparing the faecal microbiota of Caucasian children and children in rural Africa, where the diet is plant based and high in fiber content [7]. African children showed a significant enrichment of Bacteroidetes and a depletion of Firmicutes when compared with the European children. In addition, the bacteria present in the African children expressed genes related to cellulose and xylan hydrolysis. These results illustrate that these bacteria co-evolved with the polysaccharide-rich diet in Africans, which allowed them to maximize the energy intake from fibers [7].

Antibiotics can have a profound effect on the gut microbiome. For example, ciprofloxacin treatment results in a profound and rapid loss of diversity and richness of the microbiome, with a shift in the community composition as early as 3–4 days after drug initiation. One week after stopping antibiotics, the microbial communities began to return to their initial state, but the recovery was often incomplete [8].

The composition of gut microbiota is also influenced by the host genetics and immune status [9].

In health, the gut microbiome exists in ‘symbiosis’, a state of coexistence in mutual harmony, which is disturbed in disease states. A number of interesting and provocative associations between disease and microbiome are emerging, which remains to be confirmed [10]. Patients with progressive IgA nephropathy have a distinct microbiome profile, with higher percentages of some genera/species of Ruminococcaceae, Lachnospiraceae, Eubacteriaceae and Streptococcaceae [11]. The microbiome has also been implicated in kidney stone formation [12]. The gut microbiome can also produce beneficial metabolites, such as short-chain fatty acids (SCFAs) that could be kidney protective [13].

Gut Microbiome in Chronic Kidney Disease
The microbiome profile is altered in patients with CKD and in patients with end-stage renal disease (ESRD). As many as 190 microbial units differed significantly in abundance when the gut microbiome of ESRD patients was compared to that of apparently healthy controls [14]. In another study, the number of aerobic bacteria, including Enterobacteria and Enterococci species was shown to be higher in ESRD patients than in controls. Among anaerobic bacteria, hemodialysis patients had significantly higher counts.
for Clostridium perfringens and lower numbers of Bifidobacterium species [15].

**Mechanism of dysbiosis in chronic kidney disease**

Dysbiosis is an imbalance in the intestinal microbiota that precipitates changes in the usual activities of gastrointestinal tract, resulting in production of toxins and deleterious effects in the organism [16]. Several factors contribute to dysbiosis in patients with CKD, such as slowing of intestinal transit, decreases in digestive capacity and secretion of ammonia and urea into the gut [17]. The cause of slow colonic transit time and frequent constipation observed in CKD and particularly hemodialysis patients seems to be multifactorial. Dietary restriction and low fiber consumption, lack of activity, use of phosphate binders and co-morbidities such as diabetes and heart disease might all contribute to the greater prevalence of constipation in these patients [18].

Slowing of the intestinal transit permits proliferation of bacteria. Impaired protein digestion results in undigested protein being delivered to the colon, which also causes proliferation of proteolytic bacteria. There is a minimal increase in the serum concentration of uric acid in advanced CKD owing to CKD-induced adaptive secretion of uric acid by the colon [19]. As a result of the urea/uric acid secretion in the gut, bacterial families possessing urease, uricase, phenol and indole-forming enzymes are expanded, whereas the SCFA-forming bacteria are contracted in ESRD patients [20].

Furthermore, increased secretion of ammonia and urea into the gut changes the pH, leading to the growth of pH-sensitive bacteria, ESRD disease patients also have changes in diet, including a decrease in fiber intake, which decreases the bifidobacteria. Finally, frequent use of antibiotics and iron delivered in either oral or intravenous form could alter the microbial landscape in the gut [20].

**Clinical Consequences of Intestinal Dysbiosis**

Gut microbiota plays an important role in regulating immunity and host metabolism. Consequently, disruption of the gut microbiota has been associated with various human diseases of the immune system, gastrointestinal tract, and cardiovascular system. Both CKD and ESRD are associated with altered gut microbiome [21]. In patients with chronic renal failure, uremia has been shown to increase intestinal permeability, which together with loss of barrier function, lead to entry of live bacteria, endotoxin molecules, and gut derived uremic toxins into the systemic circulation. This results to a persistent systemic inflammation that over time will drive endothelial dysfunction, atherogenesis, and CVD [22].

A number of gut bacteria and their products are now known to be associated with CVD identified Chryseomonas, Veillonella, and Streptococcus in atherosclerotic plaques [23]. Elevated endotoxin level has also been shown to be a strong risk factor for the development of atherosclerosis in the general population [24]. CVD and mortality in patients with CKD and hemodialysis patients is associated with elevated plasma level of sCD14 (the receptor for endotoxin) [25]. Furthermore, elevated levels of indoxyl sulfate and p-cresol sulfate, two of the uremic toxins generated by gut microbes, have been associated with risk of cardiovascular mortality in patients with chronic renal failure [26].

Recent studies have revealed trimethylamine N-oxide (TMAO), choline, and betaine to be associated with heart disease [27]. TMAO is
formed in the liver from the metabolism of trimethylamine gas, a product of choline catabolism by the intestinal microbiota. TMAO is also produced from dietary carnitine, which is high in red meat and serves as another substrate for gut flora to produce TMAO [28]. Elevated TMAO level predicted an increased risk of major adverse cardiovascular events in a study involving 4007 patients undergoing elective coronary angiography [29].

More recently, gut microbiome dysbiosis has been associated with essential hypertension which is considered another causative factor for chronic renal failure. The potential role of the microbiome in regulating human BP and causing hypertension is mostly based on animal studies. One of the few human studies that looked at gut microbiome and hypertension was the gut microbiome composition analysis of patients with elevated systolic blood pressure (SBP) compared with those with normal SBP. Results of this study revealed a decreased bacterial richness and altered bacterial compositions in patients with elevated SBP [30].

The gut microbiota can ferment dietary fibers to yield SCFAs acetate and propionate (produced by Bacteroidetes phylum members) as well as butyrate (produced by bacteria of the Firmicutes phylum) [31]. In addition to their ability to moderate immune signaling [32] and anti-inflammatory impact on both colonic epithelium and immune cells [33], SCFAs also have a vasodilation property in vitro as both butyrate and propionate can induce dilation of human colonic arteries [34]. Interestingly, the SCFA olfactory receptor 78 (Olfr78) is expressed in the kidneys and regulates BP, as shown by BP reduction of about 20 mmHg following administration of propionate to normal mice [35].

Targeted interventions to treat intestinal dysbiosis in CKD

Modulation of Gut Microbiota:

Prebiotics

A prebiotic is a non-digestible (by the host) food ingredient that has a beneficial effect through its selective stimulation of the growth or activity of one or a limited number of bacteria in the colon [36]. The candidate prebiotics include inulin, fructo-oligosaccharides, galacto-oligosaccharides, soya-oligosaccharides, xylo-oligosaccharides, and pyrodextrins. Prebiotics promote the growth of Bifidobacteria and Lactobacilli species at the expense of other groups of bacteria in the gut, such as Bacteroides species, Clostridia species, and enterobacteria [37]. Preliminary evidence indicates that prebiotic oligofructose-enriched inulin (p-inulin) promotes growth of Bifidobacteria species, mediates weight loss, reduces inflammation, and improves metabolic function [38]. Several studies reported that serum concentrations of p-cresol and indoxyl sulfate are reduced by the oral intake of p-inulin in hemodialysis patients [39].

Probiotics

Probiotics are defined by the United Nations’ Food and Agriculture Organization and the World Health Organization as “live microorganisms” that when administered in adequate amounts confer a health benefit on the host [40]. Probiotics consist of living bacteria, such as Bifidobacteria species, lactobacilli, and streptococci, that can alter gut microbiota and affect the inflammatory state. Hemodialysis patients treated with oral Lactobacillus acidophilus showed decreased serum dimethylamine, a potential uremic toxin [40].

Acarbose
Acarbose is an inhibitor of a-glucosidase enzymes in the intestinal brush-border that blocks the hydrolysis of poly- and oligosaccharides to glucose and other monosaccharides. The undigested oligosaccharides that enter the colon act as fermentable carbohydrates showed that treatment with acarbose reduces the colonic generation of p-cresol in healthy persons [42].

**Gut Microbiome Transplantation**

Transplantation of a rich pool of exogenous bacteria led to an increase in bacterial diversity and changing the microbiome of the recipients to resemble that of the donor [4].

**References**


