REVIEW ARTICLE

Gut microbiome in chronic kidney disease: challenges and opportunities

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More than 100 trillion microbial cells that reside in the human gut heavily influence nutrition, metabolism, and immune function of the host. Gut dysbiosis, seen commonly in patients with chronic kidney disease (CKD), results from qualitative and quantitative changes in host microbiome profile and disruption of gut barrier function. Alterations in gut microbiota and a myriad of host responses have been implicated in progression of CKD, increased cardiovascular risk, uremic toxicity, and inflammation. We present a discussion of dysbiosis, various uremic toxins produced from dysbiotic gut microbiome, and their roles in CKD progression and complications. We also review the gut microbiome in renal transplant, highlighting the role of commensal microbes in alteration of immune responses to transplantation, and conclude with therapeutic interventions that aim to restore intestinal dysbiosis. (Translational Research 2016;■:1–14)

Abbreviations: ■■■ = ■■■

INTRODUCTION

Human gut is home to approximately 100 trillion microorganisms and has about 100 times the number of genes in our genome.[1] In health, gut microbiota exists in "symbiosis" and provides the host with a wide range of metabolic capabilities such as breakdown of indigestible plant polysaccharides (PSA),[2] synthesis of vitamins,[3] biotransformation of conjugated bile acids, and degradation of dietary oxalates.[4] Postnatal colonization of the intestine by bacteria educates our immune system and reduces allergic responses to food and environmental antigens. Chronic kidney disease (CKD) is a global public health problem affecting up to 10% of the population.[1] "Microbiome-centric theory of CKD progression" proposes that initial adaptive changes in gut microbiome become maladaptive in later stages of CKD, leading to CKD-related complications.[5] Dysbiosis in patients with CKD is being increasingly recognized as a potential therapeutic target, but the science is in its nascent state. In this review, we will discuss the recent advances in the field of gut microbiome and how it could revolutionize management of CKD-related complications.

Gut microbiome in health—symbiosis. Advances in sequencing technology and bioinformatics have revealed the complexity of human microbiome. The human microbial community (microbiota) includes bacteria, Archaea, viruses, phages, fungi, and other microbial Eukarya. Findings from the Human Microbiome

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Project suggest that each individual's microbiome is unique, each niche is characterized by one or a few signature taxa, and diversity is greatest in the gut with little variation over time.[6,7] The predominant bacterial groups in the human gastrointestinal tract are bacteroidetes, firmicutes, and actinobacteria.[8]

Acquisition of the human microbiota begins at birth, and it undergoes dynamic adaptive changes over time that are influenced by age, sex, race/ethnicity, geography, diet, and host genetics. Findings from the Twins UK study indicate that abundance of many microbial taxa are influenced by host genetics.[8] Thaiss et al[9] showed that intestinal microbiota exhibits diurnal oscillations that are influenced by feeding rhythms, leading to time-specific compositional changes. Metagenomic sequencing of fecal samples demonstrated that bacterial genes involved in energy metabolism and protein synthesis are abundant during the day, whereas those genes related to detoxification become abundant at night.[9] Indeed, gut microbial ecosystem is considered as an organ by itself, whose metabolic capacity exceeds that of liver.

Diet has a significant impact on the gut microbiome profile. Muegge et al[10] studied gut microbiome profile in 33 mammalian species and 18 humans and noted that there is clear separation of microbiome by host diet. They reported that the difference in microbiome profile stems from differing metabolic functions required to use the diet.[10] When fecal microbiota of European children was compared to that of children from a rural African village who consume high-fiber diet, it was evident that African children showed a significant enrichment in bacteroidetes and depletion in firmicutes, with a unique abundance of bacteria from the genus *Prevotella* and *Xylanibacter*, known to contain a set of bacterial genes for cellulose and xylan hydrolysis.[11] It appears that gut microbiota in African children has coevolved with the PSA-rich diet, allowing them to maximize energy intake from fibers.

Gut microbiome in disease—dysbiosis. Dysbiosis, a term first described by Elie Metchnikoff,[12] refers to an imbalanced intestinal microbial community with quantitative and qualitative changes in the composition and metabolic activities of the gut microbiota. The "Hygiene hypothesis" and the "Old Friends hypothesis" propose that alterations in gut microbiome induced by hygienic practices may be related to the recent surge in autoimmune diseases and allergic diseases. Indeed, the declining incidence of infectious diseases over the past 50 years appears to be coinciding with the steady rise in the incidence of allergic and autoimmune diseases in developed countries.[13] Dysbiosis of the gut microbiota has been implicated in the pathogenesis of both intestinal and extraintestinal disorders such as allergy and asthma,[14] obesity,[15] diabetes,[16] cardiovascular disease (CVD), and cancer.[17] Emerging evidence indicate that dysbiosis may underlie the obesity epidemic. Chevalier et al[18] show that cold exposure induces marked increase in the ratio of firmicutes to bacteroidetes and almost a complete loss of verrucomicrobia species, including *Akkermansia muciniphila*, which has been shown to promote energy harvest in a mouse model of obesity.[19]

Gut microbiome as a potential source of uremic toxins. In 1965, Einheber and Carter[20] showed that germfree anephric mice survived longer than anephric mice with intact gut microbiome. Yokoyama[21] showed that sterilizing the intestine by antibiotics decreased the fecal and urinary excretion of phenolic and aromatic bacterial metabolites in weanling pigs with normal kidney function. Gut microbiota has been shown to contribute to the generation of several uremic toxins (Table1). Using untargeted metabolomic mass spectrometry, Wikoff et al[91] reported that the presence of several protein-bound uremic toxins, such as indoxyl sulfate (IS), hippuric acid, and phenylacetic acid, are dependent on the presence of gut microflora. Aronov et al[92] studied the plasma samples from hemodialysis patients with and without colons and demonstrated that a number of solutes are absent or present only in low concentrations in subjects without colon, suggesting a colonic origin of these molecules. Impaired protein assimilation in uremia leads to influx of undigested proteins into the distal intestine, which favors the proliferation of proteolytic bacteria.[93] Increased protein fermentation results in generation of potentially toxic metabolites such as, ammonia, phenols, amines, indoles, and thiols.[94] Poesen et al[95] studied the stool metabolomics in 20 hemodialysis patients, 20 healthy subjects, and 20 household contacts. Although a clear discrimination was noted between unrelated controls and end-stage renal disease (ESRD) patients, they noted similarity between hemodialysis patients and their household contacts, leading them to conclude that the CKD-related differences in the human colonic microbial metabolism can be attributed to a large extent to dietary restrictions and to a lesser extent to loss of renal function. However, they did not assess the dietary pattern in this study. Furthermore, in the same study, they noted that the CKD and non-CKD rats that were fed with same diet had significantly different stool metabolomic profile.[95]

Prior studies by Vaziri et al[96] have demonstrated extensive change in the structure and function of the gut microbiome in humans and animals with advanced CKD. Individuals with ESRD restrict fruits and