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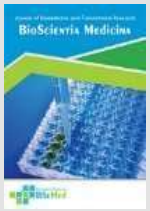

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Gut Microbiota in Chronic Kidney Disease: A Narrative Literature Review

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A B S T R A C T

Chronic kidney disease (CKD) is a growing public health problem related to loss of kidney function and cardiovascular disease as the main causes of morbidity and mortality in CKD. It is known that CKD is associated with intestinal dysbiosis. There is an influence of the gut microbiota on the gut-kidney axis and it works reciprocally: on the one hand, CKD significantly changes the composition and function of the gut microbiota. On the other hand, gut microbiota is able to manipulate the processes that cause the emergence and progression of CKD through inflammatory, endocrine and neurological pathways. Understanding the complex interactions between gut and kidney microbiota may provide novel nephroprotective interventions to prevent the progression of CKD by therapeutically targeting balance of gut microbiota composition.

1. Introduction

Chronic kidney disease (CKD) contributes to a significant burden on the health care system, society, and economy. Epidemiological studies reveal that the global prevalence of CKD is around 11% to 13%. The financial impact of CKD is up to $48 billion annually in the US. Therefore, it is important to explore its pathogenesis and prepare new treatment strategies. An abnormal intestinal environment has been revealed to be closely related to CKD. A global study reports that approximately 697 million people worldwide show an estimated reduction in glomerular filtration rate (GFR). Changes in intestinal microecology can increase the risk and influence the development of several diseases, including CKD. In this literature review, we will discuss the current understanding of the relationship between gut microbiota and CKD, the reciprocal relationship between gut dysbiosis and CKD, analyze the various mechanisms by which gut dysbiosis causes or exacerbates CKD, and explore potential strategies to improve gut microecology in CKD patients.[1,2]

The role of gut microbiota in the pathophysiology of CKD

Normal intestinal microbiota/flora has an important role in human health. There are more than 10-100 trillion microorganisms with more than 400 species of bacteria from five main bacterial phyla, namely *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria*, and *Verucomicrobia*. *Firmicutes* (*Ruminococcus, Clostridium, Lactobacillus, Eubacterium, Faecalibacterium,* and *Roseburia*) and *Bacteroidetes* (*Bacterioids, Prevotella*, and *Xylanibacter*) are the most dominant groups in healthy individuals found in the digestive tract representing

100 times the genetic material of the human genome. This is why the gut microbiota is considered an active "organ" that influences the health of its host or the human body. *Firmicutes* are gram-positive bacteria with low guanine/cytosine (G/C) content in their DNA. Most species have a rod-shaped morphology (straight or slightly curved), and their cell walls contain muramic acid. Many members of this phylum break down complex carbohydrates in the intestine that cannot be digested by endogenous enzymes. *Lactobacillus*, a probiotic bacteria that can be found in fermented milk products, causes the production of SCFAs, such as acetate, lactate, and antimicrobial molecules that prevent the colonization of intestinal pathogens. Besides *Lactobacillus*, other mutualistic bacteria from the Firmicutes phylum, such as *Faecalibacterium, Eubacterium, Roseburia,* and *Anaerostipes,* ferment carbohydrates to produce butyrate, which acts as an energy source for the host and has anti-carcinogenic and anti-inflammatory effects.[3]

Bacteroidetes are anaerobic gram-negative bacteria that colonize the entire gastrointestinal tract. One of the most common genera of this phylum, Bacteroids, is an anaerobic species, resistant to bile, and does not form spores. They ferment complex carbohydrates and produce volatile fatty acids that are a source of energy for the host. Another significant genus of bacteria in the gut belonging to the phylum *Bacteroidetes* is *Prevotella*. The prevalence of *Prevotella* is higher in individuals who consume a plant-based diet than an animal-based diet. This high-fiber diet acts as a prebiotic and stimulates the growth of mutualistic bacteria. The gut microbiota of Americans and Europeans who consume Western diets tends to be dominated by *Bacteroides* and *Clostridiales*, while rural populations with high-fiber, low-protein diets tend to be dominated by *Prevotella*. However, studies also show that *Prevotella* colonization results in metabolic changes in the microbiota, leading to decreased IL-18 production and consequent increased susceptibility to mucosal inflammation and potential systemic autoimmunity.[4]

The ratio of *Firmicutes/Bacteroidetes* (F/B) plays an important role in maintaining intestinal homeostasis, and the presence of deviations in the F/B ratio is considered dysbiosis leading to pathological conditions. While some members of both Firmicutes and Bacteroidetes are probiotics, an overall increase in *Firmicutes* is associated with obesity, and an increase in *Bacteroidetes* is associated with intestinal inflammation. The F/B ratio is important because some members of one phylum help maintain normal numbers of potentially pathogenic bacteria from other phyla. The ideal F/B ratio is 1. There is a very significant change in the F/B ratio in patients with CKD and related complications such as hypertension and obesity. In CKD patients, a high-fiber diet increases microbial biodiversity and increases *Bacteroidetes*, leading to a lower F/B ratio. This leads to improved kidney function and the importance of a balanced F/B ratio in maintaining kidney health. Intake of a high-fiber diet causes an increase in the number of SCFAs-producing bacteria, balancing the F/B ratio by increasing Bacteroidetes.

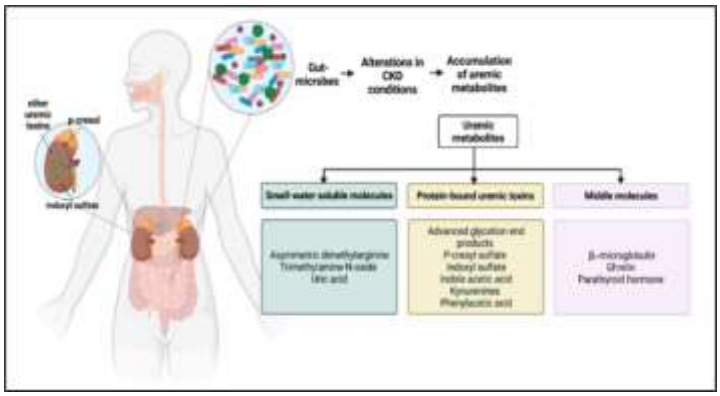

Figure 1. Results of uremic toxin metabolites.

The relationship between gut microbiota and CKD has been widely studied. When CKD occurs, the kidneys lose the ability to eliminate catabolites produced from the body's metabolism and synbiote (gut microbiota). Several substances fall into the category of uremic toxins. The most frequently studied intestinal derivatives are p-cresyl sulfate (p-CS), indoxyl sulfate (IS), indole 3 acetic acid (IAA), and trimethylamine N-oxide (TMAO). There are also derivatives from the catabolism of animal products, such as choline, phosphatidylcholine, carnitine, and betaine. There is mounting evidence to suggest that altered gut microbiota in CKD may contribute to increased production of gut-derived uremic toxins. The origins of uremic toxins in CKD are diverse. These toxic metabolites can be classified according to their origin in (1) uremic toxins originating from endogenous metabolism, (2) uremic toxins originating from microbial metabolism, or (3) uremic toxins originating from exogenous intake. These products are usually excreted in the feces, and although some can be absorbed and eliminated by the kidneys, they will accumulate in CKD patients. Patients with CKD typically exhibit an imbalance in the gut microbiota that favors the growth of pathological bacteria with proteolytic activity, leading to the formation of uremic toxins. All these toxins often accumulate in the early stages of CKD and stimulate inflammation and oxidative stress, thereby contributing to the development of kidney damage and increasing cardiovascular risk in CKD patients. IS is synthesized from the metabolism of dietary tryptophan, while p-CS originates from the catabolism of phenylalanine and tyrosine by anaerobic intestinal bacteria. Both IS and p-CS are capable of inducing tubulointerstitial fibrosis and glomerular sclerosis, impaired renal function, and disease progression. IS also plays a key role in endothelial dysfunction by inducing pro-inflammation.[5]

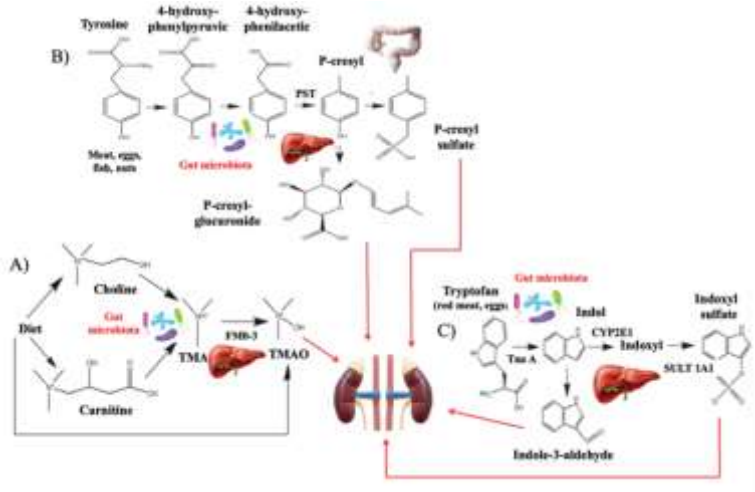

Figure 2. Metabolic pathway of uremic toxins originating from the intestine.

With the increasing progression of CKD, there is also an accumulation of toxic compounds in the bloodstream, which causes a toxic condition. There is also speculation that CKD not only causes a decrease in the elimination ability of uremic toxins but also increases their production, which is involved in the process of intestinal microbiota. Changes in the composition of the gut microbiota can be caused by many factors, such as smoking, drugs, diet, and some pathological conditions. Several studies have shown that in CKD patients, there is a change in the composition of the gut microbiota compared to healthy people. This imbalance/change is referred to as dysbiosis. Based on the substrate used by the microbiota to obtain energy, the microbiota can follow two main metabolic pathways, namely saccharolytic

(enzymes that play a role in the formation of short-chain fatty acids-SCFAs) and proteolytic (enzymes that can hydrolyze peptide bonds). Under normal circumstances, saccharolytics will be more abundant than proteolytics. CKD causes an increase in the proteolytic population (which causes increased production of ammonia and other uremic toxins such as phenols and character) and decreased saccharolysis (which causes a decrease in the formation of SCFAs).[6]

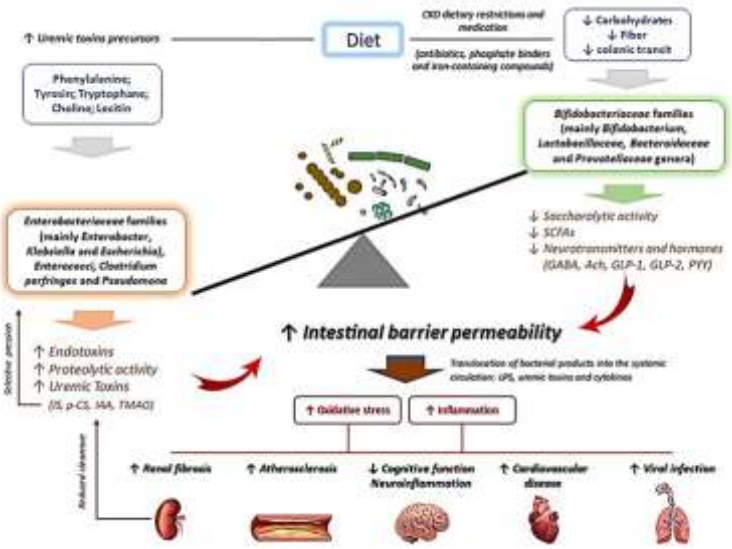

Figure 3. Pathogenesis of intestinal dysbiosis in CKD.

When pathological conditions or food imbalances occur, the lack of substrate availability causes disruption of the anabolic function of the intestinal microbiota, so that it is compensated by the use of amino acids to obtain energy and causes toxin production. During the saccharolytic fermentation process, it causes the production of SCFAs, which can inhibit the growth of bad microbes (pathobionts), protect the intestinal lumen via local and systemic endocrine, and increase anti-inflammatory activity by signaling to the immune system, including neutrophils, in patients with CKD, a vicious circle forms, namely the formation of proteolytic uremic toxin metabolites (such as p-CS and IS) and worsening renal elimination function.

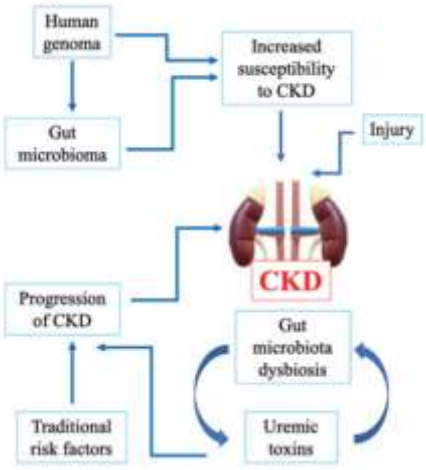

Figure 4. Bidirectional relationship between gut microbiota and CKD.

Urea is the waste product that is most commonly retained in CKD patients. It has been demonstrated that an increased influx of urea into the GI lumen favors the overgrowth of urease-expressing bacteria. This was confirmed by clinical studies, as patients with PGTA showed a predominance of urease-bearing bacterial families compared with healthy controls. Hydrolysis of urea by intestinal microbes results in the formation of large amounts of ammonia. Ammonia increases luminal pH and changes the composition of the microbiota, leading to dysbiosis. CKD patients will be exposed to antibiotics to treat vascular access and other infections. Antibiotic use impacts the gut microbiota with loss of critical taxa necessary to maintain homeostasis, loss of biodiversity, changes in metabolic capacity, and expansion of pathogens. On the other hand, long-term consumption of phosphate binders and iron-containing compounds can cause changes in the luminal environment of the GI tract and affect the existing microbial flora, leading to dysbiosis. Phosphate-binding compounds are usually given to patients with CKD to treat hyperphosphatemia, but long-term use can cause changes in the intestinal lumen. Research in vitro in the human intestine showed that iron therapy reduced levels of *Bifidobacteriaceae* and *Lactobacillaceae* (saccharolytic) and increased concentration of *Roseburia* and *Prevotella* (proteolytic), which causes a change in the dominance of saccharolytic metabolism to proteolytic.[7]

Dysbiosis is not only caused by uremia but can also be caused by local (intestinal) or systemic causes. When there is a decline in kidney function as the body's main excretory organ and the function of eliminating urea from the intestine, this causes damage to the intestinal microchemical environment. This results in an increase in intestinal pH, which creates selective pressure on the urease-positive species responsible for converting urea to ammonia. This causes degradation of the intestinal mucosal layer and changes in intestinal permeability due to damage to the system's tight junction. The consequence is that it is easy for bacteria to pass through the intestinal mucosa into the bloodstream, activating local and systemic inflammatory mechanisms. This contributes to endotoxemia and systemic inflammation.

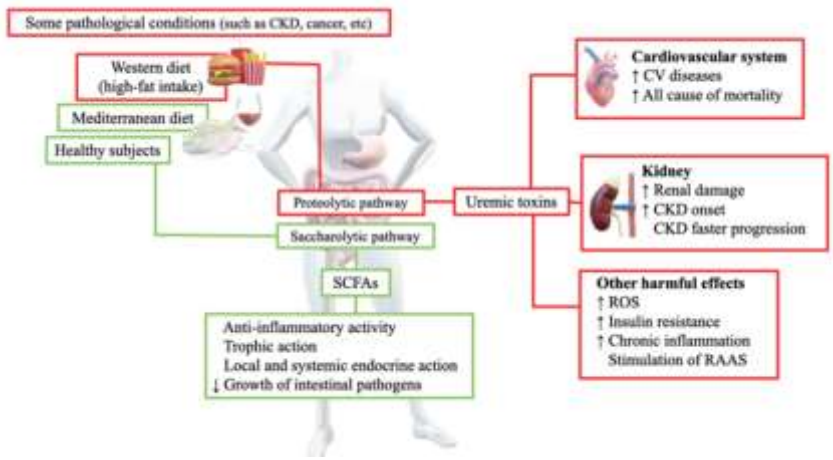

Figure 5. Impact of diet and formation of uremic toxins in the intestine.

Several scientific studies link the inflammatory state to the translocation of intestinal bacterial fragments in the systemic circulation, as indicated by the presence of DNA from intestinal bacterial species in the blood. Therefore, gut microbiota mediates systemic inflammation in CKD. In particular, Proteobacteria are involved in the inflammatory response, inducing disruption of intestinal mucosal permeability and an increase in the ratio of T cells helper 17 (Th17) against cells T regulator intestine, and promoting LPS translocation. Increasing evidence from recent years suggests that gut dysbiosis has an

important role in the pathogenesis of chronic systemic inflammation. In the context of intestinal dysbiosis, pathogenic bacteria outnumber commensal bacteria and release large amounts of immunogenic substances, including LPS and peptidoglycan, which activate the immune system of the intestinal mucosa and disrupt intestinal permeability, with translocation of bacterial products into the host circulatory system, thereby favoring the production of mediators. inflammation such as IL-6, interferon γ (IFN-γ), and tumor necrosis factor α (TNF-α). Supporting this fact, patients with type 2 diabetes and CKD (stages 4 and 5 without dialysis) show a significant increase in gram-negative bacteria such as *Proteobacteria*, *Verrucomicrobia*, and *Fusobacteria* in fecal microbiota samples. Gram-negative bacteria exhibit strong levels of the outer membrane endotoxin, LPS, which is recognized by immune cell surface receptors such as Toll-like receptor *4* (TLR4), which induces the production of pro-inflammatory cytokines through nuclear factor-*κB* (NF-κB). Serum LPS levels in this group of patients were significantly increased when compared with the healthy population and correlated with increased levels of inflammatory biomarkers such as TNFα, IL-6, and C-reactive protein (CRP). This state of chronic systemic inflammation is a major risk factor for the development of CKD and cardiovascular complications.[8,9]

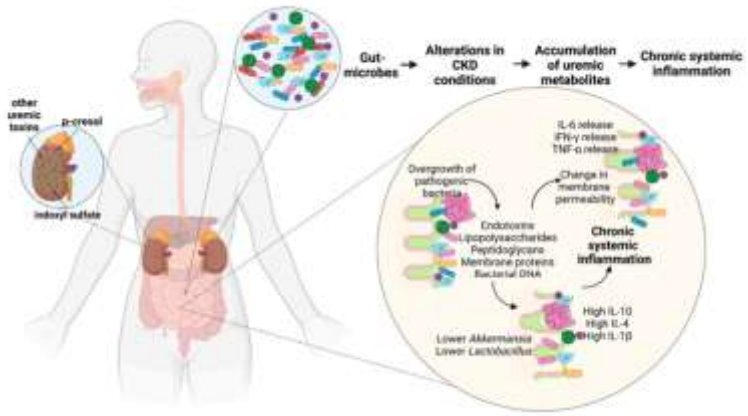

Figure 6. Gut microbiota and inflammatory mediators.

Gut-kidney axis

The gut microbiota is involved in maintaining homeostasis through constant communication with vital organs. A healthy gut environment is critical for regulating optimal protective function, and abnormal gut microbiota is associated with an increased risk of various diseases and metabolic disorders. Normal gut microbiota-derived SCFAs stimulate GLP-1 secretion, which exerts protective effects against renal oxidative stress and chronic hyperglycemia. Gut dysbiosis is characterized by an abnormal composition of the gut microbiota, leading to metabolic dysfunction, immune disorders, and endocrine abnormalities, all of which can cause or exacerbate CKD. The study reported a marked increase in the phyla *Proteobacteria*, *Fusobacteria*, *Escherichia*, *Shigella*, *Desulfovibrio*, and *Streptococcus* in patients with CKD. The relationship between CKD and intestinal dysbiosis has not been fully elucidated, and most previous studies have various limitations. Immune disorders in intestinal dysbiosis cause abnormal proliferation and differentiation of lymphocytes, leading to the production of CKD-associated autoantibodies. Pathobionts activate T cells helper and increase LPS production, thereby triggering a pro-inflammatory immune response. Furthermore, intestinal microorganisms produce metabolic proteins and choline, including indoxyl sulfate (IS), trimethylamine-N-oxide (TMAO), phenylacetylglutamine (PAG), and then P-cresyl sulfate (PCS). These metabolites play an important role in worsening renal and cardiovascular function.[10]

Gut microorganisms can also cause neuroendocrine dysfunction, which can worsen CKD. Intestinal dysbiosis impairs the energy supply to the colonic epithelium and increases epithelial permeability, leading to a kind of leaky gut. Hypertension is the most common risk factor for CKD. Intestinal dysbiosis activates the renin-angiotensin-aldosterone system, leading to hypertension. Intestinal dysbiosis in CKD patients is also involved in insulin resistance and causes dyslipidemia and triglyceridemia. Studies report that gut microbiota is also associated with other kidney diseases, such as membranous nephropathy and diabetic kidney disease. Taoet et al. proposed that gut microbiota-related biomarkers could be used to differentiate membranous nephropathy and diabetic kidney disease in patients for whom renal biopsy is contraindicated. Abnormal numbers of gut microbes have been observed in patients with IgA nephropathy. Experimental studies revealed the presence of IgA-associated nephropathy in commensal flora in mice overexpressing B cell activating factor, which is involved in IgA synthesis. The study also detected gut dysbiosis in an animal model of systemic lupus erythematosus (SLE). In addition, the study observed abnormal amounts of gut microbes in the feces of patients with SLE. Decreased diversity of gut microbiota and translocation of microbial components from the leaky gut to the liver are primarily responsible for the activation of lupus antibodies. Lupus nephritis and IgA nephropathy play a role in the development of CKD.[11]

Endocrine regulation

The gut microbiota, on the other hand, also acts like an endocrine organ by producing several hormones and neurotransmitters that influence gut endocrine activity and potentially regulate kidney function. It has been shown that changes in the gut microbiota can lead to activation of the hypothalamic-pituitary-adrenal (HPA) axis and increased secretion of serotonin and other neurotransmitters and neuroactive compounds. The HPA axis can be stimulated either directly or through immune system activation elicited by toxins produced by altered gut microbiota, such as endotoxins and peptidoglycan. In addition, species *Lactobacillaceae*, *Prevotellaceae*, and *Bifidobacteriaceae* are capable of synthesizing neurotransmitters such as γ-aminobutyric acid (GABA) and acetylcholine (ACh) to promote intestinal incretin production glucagon-like peptide-1-2 (GLP-1, GLP-2) and intestinal hormone peptide YY (PYY). Propionate, SCFAs synthesized by gut microbiota, also stimulates the release of GLP-1 and PYY. Recently, Cheema and Pluznick identified 12 metabolites in plasma and another 96 in feces that were significantly altered by infusion of angiotensin II (ANG II) in conventional mice but not in germ-free mice, suggesting that they depend on gut microbiota and may be regulated by ANG II.

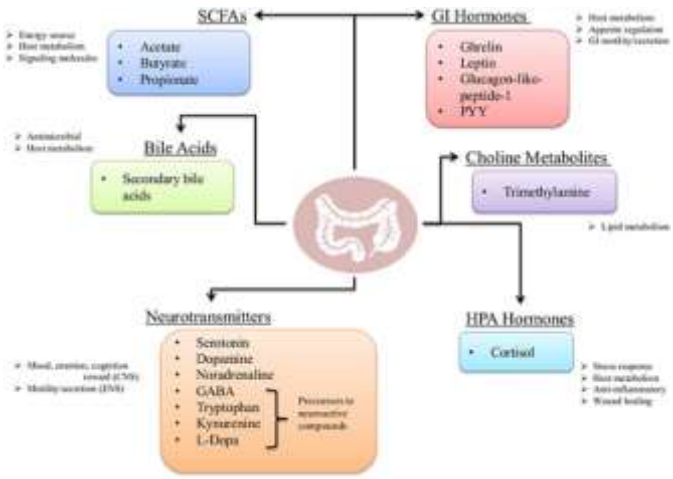

Figure 7. The gut microbiota is an endocrine organ.

All of these neurotransmitters and hormones are able to modulate kidney function. It has been proven that GABA can stimulate natriuresis and suppress renal sympathetic nerve activity, ACh can increase GFR by increasing renal vasodilation, and GLP-1 can increase GFR, diuresis, and natriuresis and reduce ANG II levels. In CKD patients, there was a significant reduction in bacterial species that modulate renoprotective properties through reducing renin-angiotensin-aldosterone and renal sympathetic system activity while increasing GFR, diuresis, and natriuresis. Ultimately, endocrine changes in sodium and blood pressure hemostasis may contribute to the onset and progression of CKD. In this way, gut dysbiosis may be considered a key feature for the progression of CKD through the alteration of the gut–kidney endocrine interactions.[12,13]

Effects of CKD on intestinal dysbiosis

The relationship between gut dysbiosis and CKD is bidirectional. CKD itself can cause changes in the normal intestinal microbiota. The use of antibiotics and certain diets consumed by CKD patients can increase the risk of intestinal dysbiosis. The typical diet of CKD patients, which is low in sodium, potassium, and phosphate, impairs the absorption of essential nutrients from food, including dietary fiber. Dietary fiber produces SCFAs, which protect against intestinal damage. Additionally, kidney function declines as CKD progresses, leading to the retention of uremic toxins. These urea-containing compounds accumulate in the intestines and blood, encouraging the colonization of microorganisms that can use urea as an energy source. This altered gut microenvironment leads to gut dysbiosis and, ultimately, leaky gut syndrome. The association of gut dysbiosis with CKD is not limited to the primary disease but extends to complications such as hypertension, cardiovascular disease, cognitive abnormalities, and mineral and bone disorders. Cardiovascular complications are the main cause of death in CKD patients. Intestinal dysbiosis promotes the development of cardiovascular events through the activation of immune complexes and the production of pro-inflammatory and cytokines reactive oxygen species (ROS).[14]

Studies reveal that increasing the number of PCS and TMAO in patients with CKD is associated with an increased risk of cardiovascular complications and a high mortality rate. Cognitive decline is another common complication of CKD, which seriously impairs patients' quality of life. Studies find that nearly 20% of patients with CKD exhibit psychiatric illness. Gut dysbiosis causes cognitive decline through effects on the neurotransmitters of the hypothalamic-pituitary-adrenal axis. Additionally, dysbiosis-induced retention of uremic toxins leads to oxidative stress and endothelial dysfunction. Some uremic toxins, such as IS, can cross the blood-brain barrier and accumulate in the brain, inducing inflammation and apoptosis in astrocytes and neuroglial tissue. Research illustrates that increased IS levels are associated with an increased incidence of cognitive dysfunction, and increased IS levels are an indicator of good mental health in CKD patients.[15]

Patients with CKD exhibit poor bone quantity, which increases the risk of fractures, especially non-vertebral fractures. Studies show that the risk of fracture increases as CKD progresses. Vascular calcification is another complication of CKD characterized by the deposition of calcium and phosphate crystals in the blood vessels and heart valves. Studies have found that approximately 60% of patients with advanced CKD have vascular calcifications, most of which appear in the tunica media layer. The presence of decreased bone quantity and vascular calcification called the calcification paradox, significantly increases the risk of morbidity and mortality in patients with CKD through bone fractures and cardiovascular disease. Intestinal dysbiosis also promotes the development of disorders of bone and mineral metabolism in CKD patients. As described previously, intestinal dysbiosis leads to the production of metabolic proteins, such as IS, TMAO, PAG, and PCS, and there is a decrease in renal clearance of these metabolites. These metabolites,

especially IS and PCS, exacerbate vascular calcification through impaired autophagic flux in endothelial cells, downregulation of miR-29b, and increased release of endothelial microparticles. Additionally, several experimental and population-based studies report an association of IS and PCS with thrombotic events, ischemic disease, atrial fibrillation, and arterial stiffness. In addition, gut dysbiosis also gives rise to the activation of pro-inflammatory cytokines, which greatly increases the risk of bone loss and vascular calcification. Damage to the intestinal epithelial barrier caused by an imbalance in the gut microbiota allows the entry of endotoxins into the circulation, triggering an inflammatory reaction. Protein fermentation metabolites are also associated with microinflammation. Pro-inflammatory cytokines promote osteochondrogenic differentiation of vascular muscle cells and decrease fetuin-A production, leading to calcification. Once formed, vascular calcification then increases the inflammatory response in the body again.[16,17]

2. Conclusion

Gut microbiota and CKD are a reciprocal relationship where the condition of CKD itself, on the one hand, influences the loss of intestinal microbial flora, and on the other hand, gut dysbiosis influences the development of CKD. The regulation of this relationship involves an imbalance between the saccharolytic (fermentative) and proteolytic (putrefactive) microbiota supporting microbiota, with increased levels of circulating uremic toxin compounds and decreased levels of nephroprotective metabolites such as butyrate, as well as the occurrence of chronic inflammation leading to the progression of CKD and its complications. Attempts to reduce the production or accumulation of nephrotoxins as well as to stimulate the production of nephroprotective metabolites through manipulation of the gut microbiota appear to be potential new therapeutic strategies to improve the survival of CKD patients.

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