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Association between gut dysbiosis and chronic kidney disease: a narrative review of the literature

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Abstract

Chronic kidney disease (CKD) is a serious non-communicable disease that poses a significant burden on healthcare and society. It is essential to devise new strategies to better treat patients with CKD. Research has illustrated that gut dysbiosis, describing an abnormal intestinal ecology, is closely associated with CKD. In this narrative review, we summarized the evidence of their mutual relationship and discussed the potential treatment options to correct gut dysbiosis in patients with CKD. Gut dysbiosis significantly increases the risk of CKD, especially in the older population. Gut dysbiosis also plays a role in CKD complications, such as hypertension, cardiovascular events, and cognitive dysfunction. The relationship between gut dysbiosis and CKD is bidirectional, and CKD itself can lead to changes in gut microecology. The usual therapies for CKD can also increase the incidence of gut dysbiosis. Meanwhile, probiotics and antibiotics are generally used to correct gut dysbiosis. Further studies are required to elaborate the association between gut dysbiosis and CKD, and more treatment options should be explored to prevent CKD in patients with gut dysbiosis.

Keywords

Chronic kidney disease, gut dysbiosis, probiotics, antibiotics, hypertension, gut microecology, prebiotics

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Introduction

Chronic kidney disease (CKD) exerts a significant burden on the healthcare system, society, and the economy. Epidemiological studies revealed that the prevalence of CKD is 10.8% in China[1] and 13% in the US,[2] whereas the global prevalence ranges 8% to 16%.[3] The financial impact of CKD is approximately $48 billion per year in the US.[4] Therefore, it is essential to explore its pathogenesis and devise new treatment strategies. An abnormal gut environment has been revealed to be closely associated with CKD. A global study reported that approximately 697 million people worldwide exhibit a reduced estimated glomerular filtration rate.[5] A normal gut flora is involved in the general well-being of humans. However, alterations of gut microecology can increase the risk of several diseases. In this narrative review, we summarized the current understanding of the association between gut dysbiosis and CKD. We searched PubMed using keywords such as, "gut dysbiosis," "chronic kidney disease," "gut dysbiosis and chronic kidney disease," and "probiotics" and selected relevant publications. We explored the mutual association between gut dysbiosis and CKD, analyzed the various mechanisms through which gut dysbiosis causes or worsens CKD, and explored potential strategies to correct gut microecology in patients with CKD in an aim to summarize the current understanding of the association between gut dysbiosis and CKD.

Evidence of gut dysbiosis involvement in CKD

Simenhoff *et al.*[6] first described an altered gut microenvironment in patients with CKD. A 1984 study by Werder *et al.*[7] reported that renal disease was rarely observed in mice raised in a pathogen-free environment. Another study found that kd/kd mice with intestinal nephritis had a significantly reduced disease incidence after being transferred to a germ-free environment.[8] Studies recorded decreased numbers of culturable anaerobic bacteria and increased numbers of culturable aerobic bacteria in the feces of patients with CKD compared with the findings in healthy individuals.[9] Viziri *et al.*[10] observed that compared with the results in sham controls, rats with induced CKD had greater bacterial abundance and increased blood pressure and serum levels of creatinine and urea.

Mechanism by which gut dysbiosis influences CKD

The association between the intestine and kidneys is termed the gut–kidney axis.[11] The gut microbiota is involved in maintaining homeostasis through constant communication with vital organs. A healthy gut environment is crucial for regulating normal barrier function, and an abnormal gut microbiota is associated with increased risks of cancer and metabolic disorders.[12] Normal gut microbiota-derived short-chain fatty acids stimulate glucagon-like peptide-1 secretion, which exerts protective effects against renal oxidative stress and chronic hyperglycemia.[13] Gut dysbiosis is characterized by an abnormal intestinal microbiota composition, which causes metabolic dysfunction, immune disorders, and endocrine abnormalities, all of which can cause or worsen CKD.[11] Studies reported an enormously increased abundance of the phyla Proteobacteria and Fusobacteria and genera *Escherichia*, *Shigella*, *Desulfovibrio*, and *Streptococcus* in patients with CVD, whereas the abundance of the genera *Roseburia*, *Faecalibacterium*, *Pyramidobacter*, *Prevotellaceae* UCG-001, and *Prevotella* was lower.[14] The association between CKD and gut dysbiosis has not been completely elucidated, and most

prior studies had various limitations. The immune disturbance in gut dysbiosis causes the abnormal proliferation and differentiation of lymphocytes, leading to the production of autoantibodies associated with CKD.[15] Pathobionts activate helper T cells and increase the production of lipopolysaccharides, thereby triggering the pro-inflammatory immune response. Furthermore, intestinal microorganisms produce metabolic proteins and choline, including indoxyl sulfate (IS), trimethylamine-N-oxide (TMAO), phenylacetylglutamine (PAG), and *p*-cresyl sulfate (PCS). These metabolites play crucial roles in deteriorating renal and cardiovascular function. Intestinal microorganisms can also cause neuroendocrine dysfunction, which can aggravate CKD. Gut dysbiosis impairs the energy supply to the colonic epithelium and increases epithelial permeability, leading to a "leaky gut."[10,14] Hypertension (HTN) is the most common risk factor of CKD. Gut dysbiosis activates the renin–angiotensin system, leading to HTN and diabetic nephropathy.[16] Gut dysbiosis in patients with CKD is also involved in insulin resistance, and it causes dyslipidemia and triglyceridemia.[17,18] Studies reported that the gut microbiota is also associated with other renal diseases, such as membranous nephropathy and diabetic kidney disease.[19,20] Tao *et al.*[21] proposed that gut microbiota-associated biomarkers can be used to differentiate membranous nephropathy and diabetic kidney disease in patients in whom renal biopsy is contraindicated. Abnormal numbers of gut microbes have been observed in patients with IgA nephropathy.[22] Experimental studies revealed the presence of commensal flora-dependent IgA nephropathy in mice overexpressing B-cell activating factor, which is involved in IgA synthesis.[23] Studies also detected gut dysbiosis in animal models of systemic lupus erythematosus (SLE).[24] In addition, studies observed abnormal numbers of gut microbes in the feces of patients with SLE.[25,26] Decreased diversity of the gut microbiota and the translocation of microbial components from the leaky gut to the liver are mainly responsible for the activation of lupus antibodies.[27] Both lupus nephritis and IgA nephropathy participate in the development of CKD.[28]

Effects of CKD on gut dysbiosis

The association between gut dysbiosis and CKD is bidirectional. CKD itself can lead to alterations of the normal gut microbiota. The use of antibiotics and the specific diet consumed by patients with CKD can increase the risk of gut dysbiosis.[29] A typical CKD diet, which is low in sodium, potassium, and phosphate, impairs the absorption of essential nutrients from food, including dietary fibers. Dietary fibers produce short-chain fatty acids, which protect against intestinal damage.[30] Furthermore, renal function declines as CKD progresses, leading to the retention of uremic toxins. These urea-containing compounds accumulate in the intestine and blood, promoting the colonization of microorganisms that can use urea as an energy source.[31] This changed gut microenvironment leads to gut dysbiosis and eventually to leaky gut syndrome.

Gut dysbiosis and CKD complications

The relationship of gut dysbiosis with CKD is not limited to the primary disease, but it extends to complications such as HTN, cardiovascular diseases, cognitive abnormalities, and mineral and bone disorders. Cardiovascular complications are the major causes of mortality in patients with CKD. Gut dysbiosis promotes the development of cardiovascular events through the activation of immune complexes and the

production of pro-inflammatory cytokines and reactive oxygen species.[32,33] Studies revealed that high levels of PCS[34] and TMAO[35] in patients with CKD are associated with an increased risk of cardiovascular complications and a high mortality rate. Cognitive decline is another common complication of CKD, which seriously impairs patient quality of life. Studies found that nearly 20% of patients with CKD exhibit psychiatric diseases.[36] Gut dysbiosis causes cognitive decline through effects on the hypothalamic–pituitary–adrenal axis and neurotransmitters.[37] Additionally, gut dysbiosis-induced uremic toxin retention causes oxidative stress and endothelial dysfunction. Some uremic toxins, such as indoxyl sulfate, can cross the blood–brain barrier and accumulate in the brain, inducing inflammation and apoptosis in astrocytes and neuroglial tissues.[38] Research illustrated that elevated levels of IS are associated with an increased incidence of cognitive dysfunction, and elevated IS levels represent a good indicator of mental health in patients with CKD.[37,38] Further studies should be performed to elaborate the role of uremic toxins in the pathogenesis of psychiatric disorders in patients with CKD. Patients with CKD display poor bone quantity, which increases the risk of fractures, especially non-vertebral fractures.[39,40] Studies indicated that the risk of fracture increases as CKD progresses.[41] Vascular calcification is another complication of CKD that is characterized by calcium and phosphate crystal deposition in blood vessels and heart valves.[42] Studies found that approximately 60% of patients with advanced CKD have vascular calcification, which mostly arises in the tunica media layer.[43] Vascular calcification is a major risk factor for cardiovascular disease. The presence of decreased bone quantity and vascular calcification, termed the calcification paradox, significantly increased the risk of morbidity and mortality in patients with CKD through fractures and cardiovascular disease.[44] Gut dysbiosis also promotes the development of bone and mineral metabolism disorders in patients with CKD. As described previously, gut dysbiosis leads to the production of metabolic proteins, such as IS, TMAO, PAG, and PCS, and there is decreased renal clearance of these metabolites in patients with CKD. These metabolites, especially IS and PCS, aggravate vascular calcification through impaired autophagic flux in endothelial cells, miR-29b downregulation, and increased shedding of endothelial microparticles.[43] Furthermore, multiple experimental and population-based studies reported associations of IS and PCS with thrombotic events, ischemic diseases, atrial fibrillation, and arterial stiffness.[45–47] Furthermore, gut dysbiosis also elicits pro-inflammatory actions, which greatly increase the risk of decreased bone quantity and vascular calcification. The impaired gut epithelial barrier caused by the intestinal microbiota permits the entry of endotoxins into circulation, provoking an inflammatory reaction.[48,49] The metabolites of protein fermentation are also associated with microinflammation. Inflammatory cytokines promote osteochondrogenic differentiation of vascular muscle cells and decrease fetuin-A production, which suppresses calcification.[50] Once established, vascular calcification further promotes inflammatory responses in the body.

Treatment strategies to correct gut dysbiosis

The conservative management of CKD primarily involves dietary modification. Patients are encouraged to consume limited amounts of sodium, proteins, cholesterol, and potassium and increased amounts of fiber and vitamin-rich food. Diets lower in fiber, potassium, and phosphorus can cause bacterial overgrowth and increased uremic

toxin accumulation.[51] A recent study by El Amouri *et al*. observed an inverse relationship between dietary fiber intake and the levels of protein-bound uremic toxins in the pediatric CKD population, highlighting the potential benefits of high dietary fiber intake in patients with CKD.[52] Probiotics and prebiotics are being used in patients with CKD globally to correct gut dysbiosis. A laboratory study found that starch-containing prebiotics effectively improved gut dysbiosis and serum and urine metabolite levels in rats with CKD.[53] Andrade-Oliveira *et al*.[54] observed increased plasma short-chain fatty acid levels following probiotic treatment in mice with acute kidney injury. These fatty acids protected against renal ischemia. Additionally, probiotics have also been demonstrated to decrease pro-inflammatory cytokine levels in patients undergoing dialysis.[55] Studies found reduced levels of uremic *p*-cresyl following probiotic treatment.[56,57] Another study observed decreased IS levels following 5 weeks of probiotic treatment.[58] A meta-analysis by Khalesi *et al*.[59] demonstrated that probiotics effectively reduced both systolic and diastolic blood pressure. Multi-strain probiotics are more efficacious than single-strain preparations. A high daily dosage ($\geq$1011 colony-forming units) for a long duration of more than 9 weeks is usually required. Scholars believe that the combination of probiotics and prebiotics may provide better efficacy. A study by Nakabayashi *et al*. revealed that symbiotics, which are combinations of probiotics and prebiotics, decreased serum *p*-cresol levels in nine patients undergoing hemodialysis.[60] A recent study by Zhu *et al*.[61] proposed that probiotics could delay the progression of CKD after administering *Lactobacillus casei* Zhang to correct bilateral renal ischemia/reperfusion-induced gut dysbiosis in mice. Their findings illustrated that probiotics exerted their effects through altering short-chain fatty acid and nicotinamide metabolism. Another recent study by Huang *et al*.[62] indicated that multi-strain preparations of *Lactobacillus* improved renal function by reducing fibrosis-related proteins and improving intestinal barrier integrity, thereby further corroborating the notion that probiotics can delay the progression of CKD. Further studies with clinical endpoints, such as mortality and cardiovascular diseases, are required to explore the effects of probiotics in patients with CKD. Antibiotics are also occasionally used to treat an abnormal intestinal microecology. The use of antibiotics improves gut dysbiosis as well as HTN and renal function in patients with CKD. Minocycline has proven effective in reducing blood pressure and improving gut microbiota in rats with HTN.[63] Qi *et al*.[64] discovered that a combination of multiple antibiotics without any anti-hypertensive drugs reduced blood pressure by 70 mmHg in a patient with resistant HTN. Drug elimination through the kidneys can be impaired in patients with CKD; therefore, antibiotics should be used cautiously.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Ethics approval and consent to participate

Ethical approval was not required because of the nature of this study (narrative review).

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