Gut dysbiosis and kidney diseases

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Gut dysbiosis and disorders

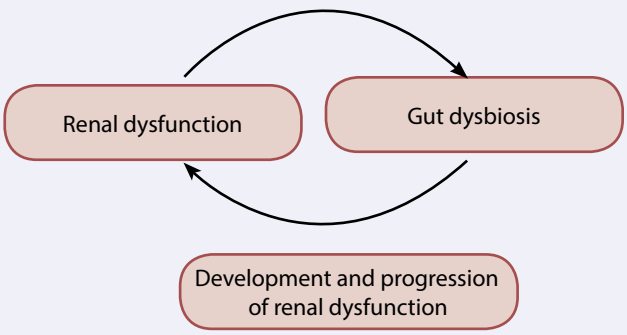
Maintenance of optimal intestinal homeostasis is critical for good health. In the last few decades, a lot has been studied on the effect of altered gut microbiome, offering us unprecedented insights into its complex association with different disorders in children and adults. Gut dysbiosis, as this altered gut microbiome is commonly referred to, can be a consequence of a wide range of causes including infections, drugs, toxins, and diet, and can lead to the development of both intestinal and extraintestinal disorders.[1] Among extraintestinal diseases, gut dysbiosis is proposed as a pathophysiological mechanism in the development of metabolic disorders (type 2 diabetes and obesity), cardiovascular (CV) disorders, cognition impairment, autism spectrum disorders, and autoimmune disorders.[1,2] More recently, evidence suggesting a connection between disruption of the normal gut microbiota and development of kidney disorders has emerged, providing proof for the existence of a "gut-kidney axis" concept. Association of gut dysbiosis with chronic kidney disease (CKD) has been proposed with considerable evidence available supporting their coexistence, and more recently its possible association with development and deterioration of acute kidney injury (AKI) has also been speculated.[3,4] These findings have paved the way for evaluation of treatment options that aim to improve renal functions by restoring dysbiosis, including pre- and probiotics and their combination therapy (synbiotics).[4]

Mechanisms involved in gut dysbiosis and kidney dysfunction

Our understanding of the pathogenic interconnection between gut microbiota and kidney diseases seems to have grown in the last few years. A bidirectional crosstalk has been speculated between the two (Figure 1).[4] Early studies focused on gut dysbiosis and CKD. Simehoff and colleagues[5] were one of the first group of investigators to confirm alteration of gut flora in patients with CKD. They compared patients with CKD and blind loop syndrome, and showed significant increase in both anaerobes and aerobes in the small intestine of CKD patients, quantitatively comparable to those in blind loop subjects. In another study[6] comparison of healthy subjects with patients of CKD showed significant reduction in the richness and structure of fecal microbiota in CKD patients compared to their healthy counterparts.

Pathophysiological mechanism linking the gut microbial balance and kidney disorders appears complex. It is suggested that increase in urea in CKD followed by its influx into the gastrointestinal (GI) tract promotes change in normal

Figure 1: Bidirectional association between gut dysbiosis and CKD



Adapted from: Chou YT, Kan WC, Shiao CC. Acute Kidney Injury and Gut Dysbiosis: A Narrative Review Focus on Pathophysiology and Treatment. *Int J Mol Sci.* 2022:26;23(7):3658.

gut flora, leading to selective pressure in favour of overgrowth of urease-producing bacteria that convert urea to ammonia. Production of ammonia changes gut pH, and hence luminal microenvironment. Since healthy gut environment maintains normal barrier functions, dysbiosis along with uremia impairs gut barrier integrity and promotes GI inflammation. Also in advanced renal failure, colon replaces kidney as the primary site of uric acid excretion, which further provides a conducive environment for overgrowth of uricase-producing bacteria. Additional factors such as altered colonic transit time associated with uremia and deficient intake of fiber-rich food in patients with CKD further aggravates intestinal dysbiosis. Resultant absorption of microbial toxins from the gut and systemic inflammation can aggravate renal dysfunction, also promoting its progression.[3] It is noteworthy that gut-derived uremic toxins (such as p-Cresyl sulfate and indoxyl sulphate) with or without CKD-induced inflammation also contribute to constipation, seen in a significant percentage of CKD patients.[7] Some of the drugs used in patients with CKD also appear to be contributors to gut dysbiosis. Long-term use of phosphate binders, commonly used in patients with CKD for correction of hyperphosphatemia, has been implicated in alteration of the delicate gut microbial balance.[8]

More recently, a similar link between AKI and gut dysbiosis has also been postulated, though the precise underlying mechanism remains unknown. It is suspected that AKI inappropriately triggers the immune response, disrupting gut barrier integrity, increasing its permeability, and predisposing to gut dysbiosis. Resulting dysbiosis-induced overproduction of gut-derived uremic toxins, insufficient generation of short-chain fatty acids (SCFA) and leakage of bacterial toxins from the gut trigger local and systemic inflammatory mechanisms, potentially deteriorating renal functions.[4]

Gut dysbiosis promotes CKD complications

In addition to association with renal impairment and its progression, gut dysbiosis also appears to increase the risk of complications, particularly in CKD (Table 1). Patients with CKD have an elevated CV risk; with a significantly higher risk of CV events in patients with early CKD. Cardiovascular complications contribute considerably to mortality in CKD. In fact, CV events rather than end-stage kidney disease is the leading cause of deaths in these patients.[9] Gut dysbiosis contributes to production of reactive oxygen species and pro-inflammatory cytokines, thereby increasing risk of CV disorders, such as hypertension. In patients with CKD, these CV events can be a significant contributor to both morbidity and mortality. Additionally, gut dysbiosis appears to increase risk of both bone and mineral metabolism disorders in CKD. Aberration in normal gut flora has also been linked to cognitive impairment, which is a well-known complication of CKD and can considerably impair quality of life in them. Finally, gut dysbiosis and retained uremic toxins has also been suggested to increase risk of mental health illnesses in patients with CKD, though this association needs to be attested in further studies.[10]

Table 1: Select complications of CKD associated with gut dysbiosis

- Hypertension
- Cardiovascular events
- Bone and mineral disorders
- Psychiatric disorders
- Cognitive decline

Adapted from: Feng Z, Wang T, Dong S, Jiang H, Zhang J, Raza HK, Lei G. Association between gut dysbiosis and chronic kidney disease: a narrative review of the literature. *J Int Med Res*. 2021 Oct;49(10):3000605211053276

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Treatment approaches to correct gut dysbiosis

Given the established association between gut dysbiosis and kidney dysfunction, there are reasons to believe that favorably modulating gut flora can improve outcomes, particularly in patients with CKD. It appears plausible that besides restoring gut microbiome balance, probiotics enhance removal of uremic toxins and their metabolites, and reduce concentration of pro-inflammatory cytokines; these factors can contribute to improvement of renal functions, or at least slow decline in renal impairment. However, good quality data to demonstrate these benefits of probiotics in CKD patients are lacking.[11] A systematic review and meta-

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analysis of online studies that focused on therapeutic effects of probiotics in patients with CKD showed its potential benefits in reducing levels of p-cresyl sulphate, a metabolite produced by intestinal bacteria and associated with worsening outcomes in CKD patients. In this study, probiotics also increased IL-6 that has been suggested to protect the intestinal epithelial barrier. This study authors recommended probiotics as a promising treatment adjunct in CKD patients.[12] In another study,[13] combined pre- and probiotics (synbiotics) intake in predialysis adult patients with CKD was also associated with reduction in p-cresyl sulphate and favorable modification of stool microbiome.[13] Resistant starch, a type of dietary fiber that acts as a substrate for microbial fermentation, has also been explored in patients with CKD. It allows survival of beneficial microbes, prevents entry of opportunist microorganisms, and can promote growth of SCFA-producing bacteria. Increase in SCFA reduces intestinal pH, thereby reducing production of proinflammatory cytokines and uremia toxins in the colon.[14] Many other treatment options that correct gut dysbiosis are being currently explored in clinical trials, and may be promising approaches for improving outcomes in CKD patients while also stemming progression of renal impairment.

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