Commentary

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Role of the Gut–kidney Axis in Chronic Kidney Disease Progression

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Introduction

Chronic Kidney Disease (CKD) is a progressive disorder characterized by the gradual loss of renal function, affecting millions worldwide and posing a major public health challenge. Traditionally, the focus of CKD research and management has been on glomerular injury, hypertension, diabetes, and other systemic risk factors. However, in recent years, the role of the gut microbiota and its interaction with the kidney termed the gut–kidney axis—has emerged as a critical area of investigation. Alterations in gut microbial composition and function are increasingly recognized as important contributors to systemic inflammation, metabolic dysregulation, and the progression of CKD. The gut–kidney axis refers to the bidirectional relationship between intestinal microbiota and kidney function, where CKD-associated changes in the gut environment promote microbial dysbiosis, and microbial metabolites and toxins exacerbate renal injury. Uremic toxins derived from gut microbial metabolism, such as indoxyl sulfate and p-cresyl sulfate, play pivotal roles in accelerating renal decline and promoting cardiovascular complications in CKD patients. Conversely, impaired kidney function alters the gut environment through uremia-induced changes in pH, motility, and intestinal permeability, further disrupting microbial balance. This interplay has important clinical implications, highlighting the potential of microbiome-targeted interventions to delay CKD progression and improve patient outcomes [1].

Description

The pathophysiology of the gut–kidney axis in CKD begins with the accumulation of uremic toxins due to impaired renal clearance. In CKD patients, microbial dysbiosis is characterized by reduced populations of beneficial bacteria such as Lactobacillus and Bifidobacterium, alongside the overgrowth of proteolytic bacteria that metabolize dietary proteins into toxic byproducts. These metabolites, including indoxyl sulfate, p-cresyl sulfate, and trimethylamine-N-oxide (TMAO), enter the bloodstream and exert nephrotoxic, pro-inflammatory, and pro-fibrotic effects. Indoxyl sulfate promotes tubular cell injury, oxidative stress, and interstitial fibrosis, while p-cresyl sulfate accelerates vascular calcification and endothelial dysfunction. TMAO has been linked to atherosclerosis, further increasing cardiovascular risk in CKD patients. This cascade of gut-derived toxicity establishes a vicious cycle where progressive renal dysfunction worsens microbial imbalance, fueling further disease progression [2].

Intestinal barrier dysfunction is another critical mechanism linking the gut microbiota to CKD progression. Uremia and systemic inflammation compromise gut epithelial tight junctions, increasing intestinal permeability and allowing the translocation of microbial products such as lipopolysaccharides (LPS) into the circulation. This phenomenon, often referred to as “leaky gut,” triggers immune activation and chronic systemic inflammation, both of which accelerate CKD progression. Elevated circulating levels of endotoxins and inflammatory cytokines contribute to endothelial dysfunction, anemia, and malnutrition commonly observed in CKD patients. Moreover, the chronic inflammatory state not only worsens kidney damage but also increases susceptibility to infections and cardiovascular complications. Therefore, restoring gut barrier integrity is considered a promising therapeutic target in the management of CKD [3].

Diet plays a central role in modulating the gut–kidney axis, influencing both microbial composition and the generation of uremic toxins. CKD patients often require dietary restrictions, particularly of protein, phosphorus, and potassium, which in turn impact microbial diversity and function. Diets high in fiber and plant-based foods support the growth of saccharolytic bacteria that produce beneficial short-chain fatty acids (SCFAs), such as butyrate, which exert anti-inflammatory and renoprotective effects. Conversely, protein-rich diets favor proteolytic fermentation, increasing the production of harmful metabolites. Clinical studies suggest that prebiotics, probiotics, and synbiotics can help restore microbial balance, reduce toxin production, and modulate inflammation in CKD patients. Additionally, emerging therapies such as oral adsorbents (e.g., AST-120) aim to reduce intestinal absorption of uremic toxins, thereby lowering systemic burden and slowing CKD progression [4].

Therapeutic strategies targeting the gut–kidney axis are expanding, with promising evidence supporting microbiome modulation as an adjunctive approach in CKD management. Probiotic supplementation has been shown to reduce levels of

indoxyl sulfate and p-cresyl sulfate in some trials, while prebiotics enhance the growth of beneficial microbes. Fecal microbiota transplantation (FMT), though still experimental in CKD, has demonstrated potential in restoring microbial diversity and improving metabolic profiles. Pharmacological interventions aimed at reducing toxin generation or enhancing clearance are also under investigation. Moreover, precision medicine approaches leveraging metagenomics and metabolomics may allow the identification of patient-specific microbial signatures, enabling tailored interventions. The integration of gut microbiome management with conventional CKD therapies, such as blood pressure control and RAAS inhibition, represents a holistic strategy to address disease progression and improve quality of life [5].

Conclusion

The gut–kidney axis plays a pivotal role in the progression of chronic kidney disease, with microbial dysbiosis, uremic toxin generation, intestinal barrier dysfunction, and systemic inflammation forming key mechanisms of interaction. Growing evidence suggests that targeting the gut microbiota through dietary modification, prebiotics, probiotics, and emerging therapies may mitigate renal decline and reduce cardiovascular risk in CKD patients. While current research remains in early stages, the gut–kidney axis represents a promising frontier in nephrology, offering novel insights into disease mechanisms and potential therapeutic strategies. By integrating microbiome-focused interventions with established CKD management approaches, clinicians may be able to slow disease progression and enhance long-term outcomes for patients worldwide.

Acknowledgment

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Conflict of Interest

None.

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