Journal of MedVerse Research & Practice
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Chronic kidney disease: The impact of intestinal microorganisms - Brief overview

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Submission Date: 29.12.2024	Accepted Date: 25.01.2025	Published Date: 31.01.2025

Abstract

Chronic kidney disease (CKD) leads to the progressive accumulation of metabolic waste products known as uremic retention solutes, which increase as renal function declines. When these solutes exert harmful effects on tissues and cellular function, they are classified as uremic toxins, contributing to the constellation of clinical and biochemical abnormalities termed uremic syndrome. Recent research highlights the role of microbial imbalances in the gut, which promote the production of metabolites such as dimethylglycine and glutarate, further exacerbating systemic toxicity. These uremic toxins have been shown to amplify inflammatory pathways, accelerate the progression of renal dysfunction, and increase the risk of cardiovascular disease, neurological impairment, and immune dysregulation. Their multifaceted impact underscores the importance of early detection, targeted therapeutic strategies, and interventions aimed at modulating gut microbiota to mitigate toxin accumulation and reduce CKD-related complications.

Keywords: Chronic Kidney Disease, Gut Microbiota

Introduction

Chronic kidney disease (CKD), which constitutes a persistent and long-term disorder affecting renal function, is defined as a medical condition that persists for a duration exceeding three months and is characterized by various structural or functional abnormalities observable within the kidneys [1–4]. These abnormalities serve as critical indicators in the assessment of kidney health. The definitive diagnosis of CKD is typically established through the identification of pathological findings or the presence of specific biochemical markers indicative of kidney damage, which may include irregularities detected in blood or urine composition, or notable deviations in laboratory test outcomes routinely employed in clinical practice to assess renal function and overall health [4].

Chronic kidney disease is a significant contributor to morbidity and mortality rates among noncommunicable diseases, and it ranks as the 10th leading cause of death globally, with an estimated worldwide prevalence ranging from 10% to 16% [1–3]. Currently, it is estimated that CKD affects over 850 million individuals worldwide, with a substantial proportion of these affected individuals residing in low- and middle-income countries where healthcare resources are often limited, thus exacerbating the challenges associated with managing and treating this prevalent condition [2].

Extensive Research

Extensive research has demonstrated that deteriorating renal function results in a significant reduction in various mechanisms essential for maintaining overall health and physiological homeostasis. These mechanisms encompass the attenuation of inflammation, mitigation of oxidative stress, regulation of autophagic processes, and enhancement of metabolic and immune functions [4,5]. As renal function declines, there is a marked impairment in these critical physiological processes.

Dysbiosis

This dysbiosis in the gut microbiome is deleterious, as it results in the production of harmful metabolites [5,9–12]. Therefore, it is imperative to develop and implement strategies aimed at improving the gut microbial composition in individuals afflicted with chronic kidney disease [7,15,16]. Under optimal and normal physiological conditions, the gut microbiota develops in a manner that is stable and balanced; however, various internal and external factors have the potential to induce both temporary and long-term alterations in its composition and functional capabilities [9,10]. Investigations conducted on healthy adult populations have elucidated the critical role played by gut microbiota in the regulation of inflammatory processes, and it has been established that perturbations in this delicate equilibrium are associated with an increased susceptibility to a variety of diseases, thereby underscoring the significance of maintaining gut health for overall well-being [11,12].

The human digestive tract harbors a complex and diverse microbiome that is predominantly composed of bacteria, but also includes archaea, viruses, phages, and fungi [10]. This intricate microbial community establishes a symbiotic relationship with the host organism, exerting a significant influence on various metabolic functions, including the fermentation of carbohydrates, the synthesis of essential vitamins, the metabolism of bile acids, and the degradation of oxalates [5,10]. Moreover, the gut microbiome plays a pivotal role in modulating immune responses and establishing connections between the functioning of the digestive tract and the overall systemic health of the individual, indicating its far-reaching implications for well-being [12].

Physiological Changes in CKD

In typical physiological conditions, there is a substantial accumulation of urea in the bloodstream, which becomes increasingly excreted through the colon as renal function progressively deteriorates [5,10]. This alteration in the patterns of excretion not only signifies a disruption of normal physiological processes but also promotes the proliferation of specific bacterial populations that possess the enzymatic capability to produce urease or uricase, both of which are enzymes that facilitate the catabolism of urea into ammonia and carbon dioxide through biochemical reactions [9,10]. The subsequent accumulation of ammonia in this altered gut environment results in a measurable increase in pH, which can compromise the structural integrity of epithelial tight junctions within the gastrointestinal tract, thereby enabling the translocation of lipopolysaccharides (LPS) from the intestinal lumen into the systemic circulation [5,14]. This translocation event ultimately initiates a complex cascade of systemic inflammatory responses that can have extensive and far-reaching health implications for individuals who are experiencing the adverse effects of chronic kidney disease [5,9,14].

Furthermore, a discernible increase in the populations of protein-fermenting gut bacteria has been observed, which are known to generate a variety of protein-bound uremic toxins that pose additional health risks [5,9,13,14]. Notable bacterial species involved in this process include those from the Clostridia genus, such as Clostridium bifermentans, Clostridium sporogenes, Clostridium clostridiforme,

and Clostridium leptum, as well as representatives from the Bacteroidetes phylum, including Bacteroides thetaiotaomicron and Bacteroides putredinis, alongside other bacterial groups like Fusobacterium nucleatum, Actinomyces israelii, Megasphaera elsdenii, and Propionibacterium acnes [5,9,14]. In contrast, individuals suffering from chronic kidney disease exhibit a reduction in beneficial bacterial species such as the Lactobacilli and Bifidobacterium species, which are typically associated with positive health outcomes [5,7,17].

Research has demonstrated that specific bacteria in the gut, notably those from the Clostridia and Bacteroidetes phyla, possess the capability to metabolize amino acids and their precursors such as tyrosine, tryptophan, L-carnitine, choline, and lysine [5,12,14]. These bacterial metabolic activities have been observed to significantly impact renal function. Furthermore, the condition of the kidneys can, reciprocally, influence the diversity and composition of the microbial communities in the gastrointestinal tract [5,12].

Dysbiosis, a term used to describe an imbalance in gut microbiota, in patients with chronic kidney disease is typically characterized by a significant reduction in microbial diversity and a notable alteration in bacterial composition, which collectively lead to an increased production of toxic metabolites that can exacerbate health issues [5,9,11,12]. For instance, which serves as a key indicator of kidney function, correlates positively with greater gut microbial diversity and the presence of beneficial bacterial genera such as Prevotella, Faecalibacterium, and Roseburia, all of which are associated with improved kidney function and overall health outcomes [5,11,12]. Conversely, a reduction in microbial diversity has been linked with an elevated urinary albumin-creatinine ratio, which is a crucial biomarker for assessing the severity of chronic kidney disease and its associated complications [5,7].

Summary

Chronic kidney disease (CKD) is a progressive disorder characterized by structural and functional kidney abnormalities lasting more than three months, affecting over 850 million people worldwide. Declining renal function disrupts key physiological processes, including inflammation regulation, oxidative stress control, metabolic balance, and immune function. CKD is strongly associated with gut microbiome dysbiosis, characterized by reduced microbial diversity, loss of beneficial species like Lactobacilli and Bifidobacteria, and overgrowth of protein-fermenting bacteria such as Clostridia and Bacteroidetes. These microbial shifts produce uremic toxins, including p-cresyl sulfate, indoxyl sulfate, trimethylamine N-oxide, dimethylglycine, and glutarate, which contribute to systemic inflammation, disease progression, cardiovascular complications, neurological impairment, and immune dysfunction. Maintaining gut microbial balance and targeting these toxins through dietary, pharmacological, or probiotic interventions may help mitigate CKD progression and improve patient outcomes [16,18-20].

Conclusion

chronic kidney disease (CKD) is strongly associated with alterations in the gut microbiome. These changes typically involve an increase in protein-degrading bacteria and a decrease in carbohydrate-fermenting species [5,9,11]. Such microbial shifts result in the production of gut-derived uremic toxins, including p-cresyl sulfate, indoxyl sulfate, trimethylamine N-oxide (TMAO), dimethylglycine, and glutarate [5,12,14]. Studies have demonstrated that these toxins play a significant role in inflammation, CKD progression, cardiovascular complications, neurological disorders, and immune system dysfunction [5,12–16].

Conflict of Interest: Nil

References

1. Centers for Disease Control and Prevention (U.S.). Chronic Kidney Disease Basics *(https://www.cdc.gov/kidneydisease/basics.html)*. Accessed 5/7/2023.
2. National Kidney Foundation. Chronic Kidney Disease (CKD) Symptoms and Causes (https://www.kidney.org/atoz/content/about-chronic-kidney-disease). Accessed 5/7/2023.
3. National Institute of Diabetes and Digestive and Kidney Diseases (U.S.). What is Chronic Kidney Disease? (https://www.niddk.nih.gov/health-information/kidney- disease/chronic-kidney-disease-ckd) Accessed 5/7/2023.
4. Chen TK, Knicely DH, Grams ME. Chronic Kidney Disease Diagnosis and Management: A Review. JAMA. 2019 Oct 1;322(13):1294-1304. doi: 10.1001/jama.2019.14745. PMID: 31573641; PMCID: PMC7015670.
5. He, M., Wei, W., Zhang, Y. *et al.* Gut microbial metabolites SCFAs and chronic kidney disease. *J Transl Med* **22**, 172 (2024).
6. Queeley GL, Campbell ES. Comparing Treatment Modalities for End-Stage Renal Disease: A Meta-Analysis. Am Health Drug Benefits. 2018 May;11(3):118-127. PMID: 29910844; PMCID: PMC5973249.
7. Sakaguchi Y, Kaimori JY, Isaka Y. Plant-Dominant Low Protein Diet: A Potential Alternative Dietary Practice for Patients with Chronic Kidney Disease. Nutrients. 2023 Feb 16;15(4):1002. doi: 10.3390/nu15041002. PMID: 36839360; PMCID: PMC9964049.
8. Shreiner AB, Kao JY, Young VB, Turnbaugh PJ, Ley RE, Mahowald MA, et al. Dicer (E-7): sc-393328. Cell [Internet]. 2015;69(1):393328.
9. Nallu A, Sharma S, Ramezani A, Muralidharan J, Raj D. Gut microbiome in chronic kidney disease: challenges and opportunities. Transl Res [Internet]. 2017;179(May):24–37.
10. Iwata Y, Wada T. Gut microbiota and chronic kidney disease. Japanese J Nephrol [Internet]. 2017;59(4):545–51.
11. Peters, B. A., Qi, Q., Usyk, M., Daviglus, M. L., Cai, J., Franceschini, N., Lash, J. C. (2023). Association of the gut microbiome with kidney function and damage in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Gut microbes*, *15*(1), 2186685. https://doi.org/10.1080/19490976.2023.2186685
12. Ramezani, A., & Raj, D. S. (2014). The gut microbiome, kidney disease, and targeted interventions. *Journal of the American Society of Nephrology : JASN*, *25*(4), 657–670. https://doi.org/10.1681/ASN.2013080905
13. Rysz J, Franczyk B, Lawisnki J, Olszeweski R, Cialkowska-Rysz A, Gluba-Brzozka

A. Uremic toxin levels are associated with gut microbiome changes in kidney transplant recipients. Transpl Int [Internet]. 2021;34(SUPPL 1):231.

14. Gut E, Soulage O, Popkov VA, Zharikova AA, Demchenko EA, Andrianova N V, et al. Citation: Gut Microbiota as a Source of Uremic Toxins. Toxins Int J Mol Sci [Internet]. 2022;2022:483.
15. Ebrahim, Z., Proost, S., Tito, R. Y., Raes, J., Glorieux, G., Moosa, M. R., & Blaauw,

R. (2022). The Effect of ß-Glucan Prebiotic on Kidney Function, Uremic Toxins and Gut Microbiome in Stage 3 to 5 Chronic Kidney Disease (CKD) Predialysis Participants: A Randomized Controlled Trial. *Nutrients*, *14*(4), 805. https://doi.org/10.3390/nu14040805

16. Farnam Nia, S., Nasri, H., Mazaheri Tehrani, S., & Rouzbahani, S. (2024). Ameliorating impact of berberine on gut microbiota in chronic kidney disease. *Journal of Renal Endocrinology*.
17. Black, AP; Anjos, JS; Cardozo, A; et al. *Does Low-Protein Diet Influence the Uremic Toxin Serum Levels From the Gut Microbiota in Nondialysis Chronic Kidney Disease Patients*. J Ren Nutr. 2018. 28(3) : 1-7

18. Marzocco, S.; Dal Piaz, F.; Di Micco, L.; et al. *Very Low Protein Diet Reduces Indoxyl Sulfate Levels in Chronic Kidney Disease*. Blood Purif. 2013. 35 : 196-201
19. Rocchetti, M; Di lorio, BR; Vacca, M; et al. *Ketoanalogs' Effect on Intestinal Microbiota Modulation and Uremic Toxins Serum Levels in Chronic Kidney Disease (Medika2 Study)*. J Clin Med. 2021. 10 (4) : 840.
20. Guldris, SC; Parra, EG; Amenos, AC. *Gut Microbiota in Chronic Kidney Disease*. Nefrologia. 2017. 37(1) : 9-19.