

Investigating the Kidney–Gut–Brain Axis in CKD: Uremic Toxins and Brain Microhemorrhages

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Abstract

Chronic kidney disease (CKD) is increasingly recognized as a systemic disorder that extends beyond renal impairment to influence gastrointestinal and neurological health. Disturbances in the gut microbial ecosystem promote the accumulation of protein-bound uremic toxins, including indoxyl sulfate (IS), p-cresyl sulfate (pCS), and trimethylamine N-oxide (TMAO), which have been implicated in vascular dysfunction and cerebrovascular injury. However, the mechanisms linking these metabolites to cerebral microhemorrhages remain incompletely understood. This study investigated the kidney–gut–brain axis using an adenine-induced murine model of CKD and a complementary cohort of patients receiving maintenance hemodialysis. Experimental animals were provided with a high-amino-acid diet to enhance the production of microbial toxin precursors, while a subset received broad-spectrum antibiotics to suppress intestinal microbial activity. Renal function, circulating uremic toxin concentrations, behavioral performance, gut microbial composition, and histopathological evidence of cerebral microhemorrhages were comprehensively evaluated. Clinical findings were validated through the analysis of archived serum specimens and neuroimaging records from dialysis patients. CKD produced marked deterioration in renal function accompanied by significant elevations in circulating IS, pCS, and TMAO. These metabolic disturbances were associated with impaired locomotor performance and a substantially greater burden of cerebral microhemorrhages compared with healthy controls. Dietary amino acid enrichment selectively amplified circulating TMAO concentrations, whereas suppression of intestinal microbiota significantly reduced all measured uremic toxins. Distinct sex-related differences were observed, with TMAO demonstrating a stronger relationship with cerebral microhemorrhage severity in male mice, while pCS exhibited a closer association in females. Antibiotic-mediated reduction of toxin production was accompanied by improvements in cognitive performance, particularly in working memory. Microbiome profiling identified disease-associated shifts in bacterial taxa, including increased abundance of *Lactobacillus* and *Ileibacterium*, without major alterations in overall microbial diversity. In the clinical cohort, elevated serum TMAO concentrations correlated with a higher prevalence of lobar cerebral microbleeds.

Keywords: kidney–gut–brain axis; chronic kidney disease; gut microbiota; uremic toxins; indoxyl sulfate; p-cresyl sulfate; trimethylamine N-oxide; cerebral microhemorrhages; neurovascular injury; cognitive dysfunction; microbiome; hemodialysis

Introduction

Chronic kidney disease (CKD) is a progressive disorder characterized by irreversible loss of renal function that affects millions of people worldwide. Although the kidneys are primarily responsible for maintaining fluid and electrolyte balance, CKD exerts systemic effects that extend to multiple organs, including the gastrointestinal tract and the central nervous system. Increasing evidence indicates that neurological complications such as cognitive impairment, depression, cerebrovascular disease, and cerebral microhemorrhages are more prevalent among patients with advanced CKD than in the general population. These complications contribute significantly to reduced quality of life, increased hospitalization, and higher mortality rates [1].

Recent investigations have highlighted the existence of a functional kidney–gut–brain axis, a bidirectional communication network involving renal function, intestinal microbiota, microbial metabolites, immune signaling, and neural pathways. Declining kidney function promotes intestinal dysbiosis, allowing excessive production and systemic accumulation of gut-derived uremic toxins. These metabolites trigger oxidative stress, endothelial dysfunction, chronic inflammation, and disruption of the blood–brain barrier, thereby increasing susceptibility to cerebral microvascular injury. Understanding the mechanisms underlying this complex interaction may provide new therapeutic opportunities for preventing neurological complications in CKD [2].

Gut Microbiota Dysbiosis and Uremic Toxin Production in Chronic Kidney Disease

The gastrointestinal microbiome consists of trillions of microorganisms that play fundamental roles in nutrient metabolism, immune regulation, and maintenance of intestinal barrier integrity. Under healthy physiological conditions, the intestinal microbial community remains balanced and supports host homeostasis. However, CKD profoundly alters the intestinal environment through metabolic acidosis, dietary restrictions, delayed intestinal transit, accumulation of urea, and frequent medication use. These changes favor the growth of bacteria capable of producing toxic metabolites while reducing populations of beneficial short-chain fatty acid–producing microorganisms [3-7].

Among the most clinically relevant microbial metabolites are indoxyl sulfate (IS), p-cresyl sulfate (pCS), and trimethylamine N-oxide (TMAO). Indoxyl sulfate is generated through bacterial metabolism of dietary tryptophan, whereas p-cresyl sulfate originates from tyrosine and phenylalanine fermentation. TMAO is produced following microbial conversion of dietary choline and carnitine into trimethylamine, which is subsequently oxidized in the liver. As kidney function declines, renal clearance of these compounds becomes impaired, resulting in progressive accumulation within the circulation. Elevated concentrations

of these toxins contribute not only to cardiovascular disease progression but also to systemic inflammation and endothelial injury, establishing a mechanistic link between intestinal dysbiosis and neurological dysfunction [8].

Pathophysiological Mechanisms Linking the Kidney–Gut–Brain Axis to Cerebral Microhemorrhages

The kidney–gut–brain axis represents a complex biological network through which microbial metabolites influence cerebral vascular health. One of the primary mechanisms involves persistent systemic inflammation initiated by circulating uremic toxins. These molecules activate inflammatory signaling pathways, stimulate cytokine production, and promote oxidative stress within vascular endothelial cells. Chronic endothelial injury subsequently compromises cerebral microvascular integrity [9,10].

Another important mechanism involves disruption of the blood–brain barrier. Increased oxidative stress weakens endothelial tight junctions, allowing inflammatory mediators and toxic metabolites to penetrate brain tissue. The resulting neuroinflammatory response activates astrocytes and microglia, further amplifying neuronal injury and vascular damage. Repeated exposure to these pathological processes contributes to the development of cerebral microhemorrhages, which are recognized as imaging markers of cerebral small vessel disease.

Experimental evidence further suggests that TMAO enhances platelet activation and thrombosis while promoting vascular inflammation. Indoxyl sulfate accelerates endothelial senescence and reactive oxygen species generation, whereas p-cresyl sulfate induces vascular stiffness and inflammatory cell recruitment. These mechanisms collectively impair cerebral autoregulation and increase the vulnerability of fragile cerebral capillaries to rupture, thereby facilitating the formation of brain microhemorrhages [11].

Experimental and Clinical Evidence Supporting Kidney–Gut–Brain Interactions

Animal studies have substantially advanced understanding of the kidney–gut–brain axis. Experimental CKD models consistently demonstrate significant elevations of circulating uremic toxins accompanied by alterations in gut microbial composition, impaired cognitive performance, and increased cerebral microvascular injury. Dietary manipulation that increases amino acid availability enhances microbial production of TMAO, whereas suppression of intestinal microbiota with antibiotics or probiotic interventions reduces toxin concentrations and improves neurological outcomes. These findings suggest that microbial metabolism plays a direct role in CKD-associated brain injury [12-15].

Clinical investigations provide complementary evidence. Patients undergoing maintenance dialysis exhibit markedly elevated serum concentrations of IS, pCS, and TMAO compared with healthy individuals. Advanced neuroimaging techniques have identified a higher prevalence of cerebral microbleeds and white matter abnormalities in these patients. Several observational studies report associations between circulating TMAO levels and cerebrovascular events, cognitive decline, and increased mortality. Although causality has not yet been fully established, accumulating evidence strongly supports the contribution of gut-derived metabolites to neurovascular dysfunction in CKD. Emerging microbiome sequencing studies further demonstrate disease-associated alterations in bacterial taxa, indicating that intestinal microbial composition may serve as both a biomarker and therapeutic target.

Therapeutic Perspectives and Future Directions

Targeting the kidney–gut–brain axis represents a promising strategy for reducing neurological complications associated with CKD. Dietary interventions aimed at increasing dietary fiber while limiting excessive intake of protein, choline, and carnitine may decrease production of harmful microbial metabolites. Supplementation with probiotics, prebiotics, or synbiotics has shown potential for restoring microbial balance and lowering circulating uremic toxin concentrations. Oral adsorbents and novel toxin-binding therapies may further reduce systemic exposure to protein-bound uremic toxins that are poorly removed during conventional dialysis [16].

Advances in microbiome-based therapeutics, including precision probiotics, engineered bacterial strains, and fecal microbiota transplantation, are being explored as innovative approaches for modulating intestinal microbial metabolism. Improvements in dialysis technology and preservation of residual kidney function may also enhance toxin clearance and reduce neurovascular injury. Future research should focus on large multicenter clinical trials integrating microbiome analysis, metabolomics, neuroimaging, and cognitive assessment to establish causal relationships and identify personalized therapeutic strategies. A deeper understanding of kidney–gut–brain interactions may facilitate the development of targeted interventions to improve neurological health and overall outcomes in individuals living with chronic kidney disease.

Conclusion

These findings provide evidence that gut microbiota-derived uremic toxins contribute to neurovascular injury through disruption of the kidney–gut–brain axis in CKD. The observed associations between microbial metabolites and cerebral microhemorrhages highlight the gut microbiome as a potential therapeutic target for reducing neurological complications in individuals with chronic kidney disease.

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