

The Microbiota–Tryptophan–Kidney–Brain Axis: Linking Gut Dysbiosis, Uremic Toxins, and Depression in Chronic Kidney Disease

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1. Abstract

Chronic kidney disease (CKD) is increasingly recognized as a systemic disorder involving complex interactions among the kidney, gastrointestinal tract, immune system, and central nervous system. Depression is highly prevalent in CKD and is associated with impaired quality of life and adverse clinical outcomes. Although psychosocial stressors remain important contributors, emerging evidence supports a biological connection between gastrointestinal dysbiosis, altered tryptophan metabolism, accumulation of gut-derived uremic toxins, and neuroinflammation. CKD alters the intestinal environment, promoting microbial dysbiosis, impaired epithelial barrier integrity, and increased generation of gut-derived metabolites. Tryptophan occupies a central position within this network because it is metabolized through serotonin, kynurenine, and microbial indole pathways. CKD-associated inflammation favors kynurenine pathway activation, whereas microbial metabolism generates indole derivatives that can be converted to protein-bound uremic toxins such as indoxyl sulfate (IS). Impaired renal clearance further amplifies their systemic accumulation. Experimental evidence suggests that these metabolites may affect the brain through aryl hydrocarbon receptor signaling, oxidative stress, blood–brain barrier dysfunction, glial activation, and altered neurotransmission. Emerging longitudinal human evidence further links selected gut-derived uremic toxins with depressive symptom burden, although causality remains unproven. This review proposes the microbiota–tryptophan–kidney–brain axis as an integrated

framework linking gastrointestinal dysbiosis with depression in CKD and discusses potential therapeutic implications.

2. Introduction

Chronic kidney disease affects multiple organ systems beyond the kidney and is accompanied by cardiovascular, metabolic, neurological, gastrointestinal, and psychiatric complications. Depression represents one of its most clinically important nonrenal manifestations. A recent systematic review and meta-analysis estimated that depression affects approximately one-quarter of individuals with CKD, with a particularly high burden among patients receiving dialysis [1]. Depressive symptoms and incident depression in CKD have been associated with cardiovascular events, hospitalization, kidney disease progression, and mortality [2,3].

Traditional explanations emphasize treatment burden, fatigue, sleep disturbance, functional impairment, dietary restrictions, and socioeconomic stress. These factors remain important; however, biological mechanisms involving gut dysbiosis, altered tryptophan metabolism, uremic toxins, systemic inflammation, and neuroinflammation have increasingly been recognized [4-8].

Tryptophan provides a particularly compelling biochemical link between these systems. This essential amino acid is metabolized through interconnected serotonin, kynurenine, and microbial indole pathways [8,9]. Kidney dysfunction may alter these pathways through systemic inflammation, microbial dysbiosis, and impaired metabolite clearance. Accordingly, the microbiota–tryptophan–

kidney–brain axis may provide a useful framework for understanding how gastrointestinal and renal dysfunction contribute to the biological vulnerability underlying depression in CKD.

3. Gut Dysbiosis and Intestinal Barrier Dysfunction in CKD

The intestinal microbiome undergoes substantial ecological and functional changes as kidney function declines. CKD-associated dysbiosis is characterized by alterations in microbial composition, reduced abundance of beneficial saccharolytic bacteria, increased proteolytic fermentation, and greater microbial capacity to generate potentially toxic metabolites [4-7]. Dietary restrictions, reduced fiber intake, constipation, medication exposure, intestinal urea influx, and the uremic environment may all contribute.

These alterations establish a bidirectional gut–kidney cycle. Increased diffusion of circulating urea into the intestinal lumen and its bacterial conversion to ammonia can alter luminal conditions and impair epithelial tight junction integrity [5,6]. Reduced production of short-chain fatty acids (SCFAs), particularly butyrate, may further compromise epithelial barrier function. Consequently, bacterial products such as lipopolysaccharide and microbial metabolites can enter the systemic circulation and potentially contribute to chronic inflammation.

Greater proteolytic fermentation also increases the generation of precursors of indoxyl sulfate, p-cresyl sulfate, indole-3-acetic acid, and other uremic solutes [7]. Because renal clearance is progressively impaired, these metabolites accumulate with declining kidney function. The gastrointestinal tract therefore becomes an active contributor to the biochemical phenotype of uremia rather than merely an organ secondarily affected by CKD.

4. Tryptophan as the Metabolic Hub

Tryptophan metabolism provides a mechanistic intersection between gastroenterology, nephrology, and psychiatry. Three principal pathways are particularly relevant [8–13].

A relatively small proportion of tryptophan enters the serotonin pathway, producing serotonin and subsequently melatonin. Although peripheral serotonin does not freely cross the blood–brain barrier (BBB), gut microbial activity can influence tryptophan availability and host serotonergic signaling [8,9]. Changes in substrate availability may therefore indirectly affect biological processes involved in mood, sleep, appetite, and cognition.

Most host tryptophan is metabolized through the kynurenine pathway. Inflammatory mediators stimulate indoleamine 2,3-dioxygenase (IDO), shifting tryptophan metabolism toward kynurenine and its downstream metabolites [10,11]. CKD is associated with reduced circulating tryptophan and increased kynurenine pathway activity, including accumulation of kynurenine, kynurenic acid, and quinolinic acid [10,11]. Importantly, patients receiving maintenance hemodialysis show markedly elevated kynurenine concentrations, and higher kynurenine has been associated with greater depressive symptom and fatigue scores [12].

The third route depends directly on the intestinal microbiota. Bacterial tryptophanase converts dietary tryptophan to indole, which

is absorbed and metabolized in the liver to indoxyl sulfate [8,13,14]. Other microbial metabolites include indole-3-acetic acid and multiple aryl hydrocarbon receptor (AhR)-active derivatives. Some microbial indoles participate in intestinal homeostasis, whereas excessive accumulation of particular metabolites in CKD may exert systemic toxicity. Thus, CKD may produce metabolic reprogramming of tryptophan rather than a simple increase or decrease in its metabolism.

5. Indoxyl Sulfate and Brain Dysfunction: Experimental Evidence

Indoxyl sulfate represents one of the clearest biochemical connections between intestinal microbial metabolism and impaired kidney clearance. Its precursor originates from bacterial metabolism of dietary tryptophan, whereas its systemic accumulation is strongly dependent on renal elimination. IS is highly protein-bound and is therefore incompletely removed by conventional dialysis [14-16].

IS has traditionally been investigated as a nephrovascular toxin. It promotes oxidative stress, endothelial dysfunction, inflammation, and renal fibrosis, and higher concentrations have been associated with vascular disease and adverse outcomes in CKD [15,16]. Increasing experimental evidence suggests that its toxicity may extend to the central nervous system.

IS is an endogenous agonist of the aryl hydrocarbon receptor [17]. Experimental studies demonstrate that IS can induce reactive oxygen species, activate AhR- and NF- κ B-related signaling, disturb antioxidant defenses, and promote inflammatory responses in astrocytes and microglia [18,19]. Experimental renal dysfunction is also associated with disruption of BBB integrity mediated partly through AhR activation [20].

Animal studies provide further biological plausibility. Increased IS exposure has been associated with cerebral accumulation, oxidative stress, altered serotonin and brain-derived neurotrophic factor signaling, neuroinflammation, cognitive abnormalities, and depression-like behaviors [21]. These findings support a potential kidney–brain mechanism; however, they should not be interpreted as evidence that IS directly causes depression in humans.

6. Human Evidence Linking Uremic Toxins and Depression

Human evidence is emerging but remains heterogeneous.

An earlier cross-sectional study involving 209 patients receiving maintenance hemodialysis found that approximately one-quarter met criteria for depression. Unexpectedly, depression was associated with lower, rather than higher, total IS concentrations [22]. The authors noted that the underlying mechanism was uncertain. Nutritional status, protein intake, dialysis-related factors, residual kidney function, and differences between total and free toxin concentrations may contribute to this counterintuitive association.

More recently, longitudinal evidence has strengthened the possibility that selected gut-derived uremic toxins are associated with depressive symptom burden. In the CKD-REIN cohort, involving more than 2,000 patients with nondialysis CKD followed longitudinally, higher concentrations of IS and indole-3-acetic acid

were associated with greater depressive symptom burden, whereas phenylacetylglutamine was associated with worsening depressive symptoms over time [23].

These apparently divergent observations are important. They suggest that relationships between uremic toxins and depression may vary according to CKD stage, dialysis status, nutritional state, residual kidney function, toxin characteristics, and study design. They also reinforce the distinction between association and causation. Current human evidence does not establish IS as a direct cause of depression; rather, it supports the possibility that gut-derived uremic metabolites participate in a broader biological environment associated with depressive symptoms.

The broader concept of a gut–brain–kidney axis has recently gained attention [24]. The specific contribution of tryptophan metabolism may refine this framework by providing identifiable molecular intermediates connecting intestinal microbial metabolism, impaired kidney clearance, systemic inflammation, and brain function.

7. Kynurenine, Neuroinflammation, and Depression

The kynurenine pathway provides a complementary mechanism independent of, but interacting with, microbial indole metabolism. Chronic low-grade inflammation can stimulate IDO activity, reducing tryptophan availability while increasing kynurenine production [10–12].

Downstream metabolites have markedly different neurobiological properties. Kynurenine acid has NMDA-receptor antagonistic and potentially neuroprotective properties, whereas quinolinic acid can promote NMDA-receptor activation, excitotoxicity, oxidative stress, and neuroinflammation [10,11,13]. Renal dysfunction may amplify these abnormalities through both enhanced inflammatory pathway activation and impaired metabolite elimination.

These mechanisms overlap with contemporary biological models of depression. Gut dysbiosis, systemic inflammation, altered tryptophan availability, glial activation, and disturbed serotonergic and glutamatergic signaling have all been implicated in mood disorders [8,9,13]. CKD may therefore create a particularly complex environment in which intestinal dysbiosis increases microbial metabolite production, renal failure reduces metabolite clearance, and systemic inflammation simultaneously redirects host tryptophan metabolism toward the kynurenine pathway.

8. The Microbiota–Tryptophan–Kidney–Brain Model

Collectively, these observations support an integrated model rather than separate gut–kidney and gut–brain axes (Figure 1).

CKD alters the intestinal ecosystem and epithelial barrier, increasing exposure to microbial metabolites and inflammatory products. At the same time, reduced kidney function limits elimination of protein-bound and other uremic solutes. Systemic inflammation further activates host kynurenine metabolism.

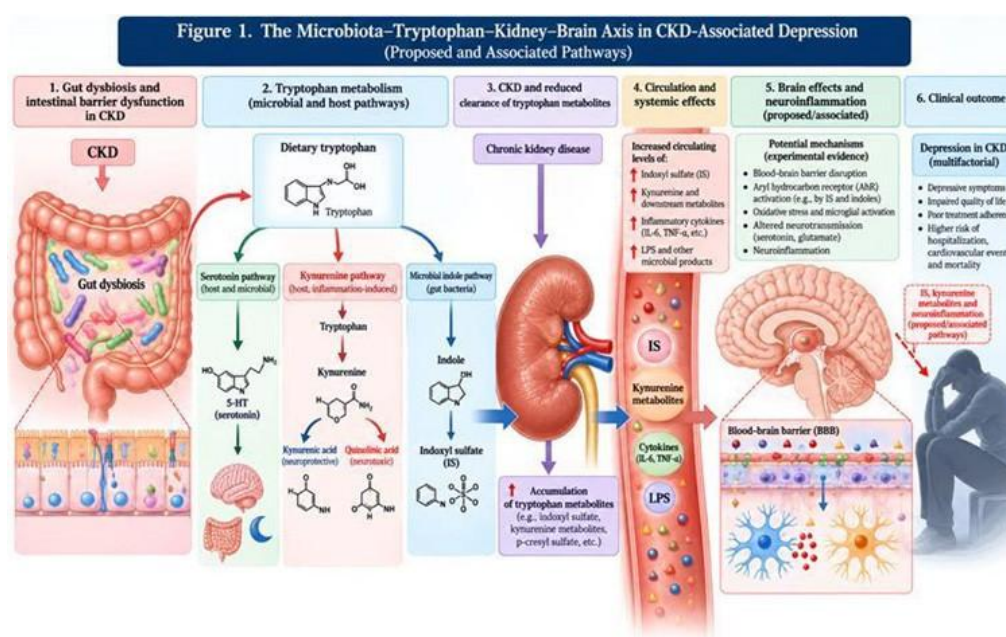


Figure 1: Proposed microbiota–tryptophan–kidney–brain axis in chronic kidney disease-associated depression. Chronic kidney disease (CKD) promotes gut microbial dysbiosis and intestinal barrier dysfunction, potentially increasing systemic exposure to microbial products and altering tryptophan metabolism. Tryptophan is metabolized through serotonin, host kynurenine, and microbial indole pathways. Gut-derived indole is converted in the liver to indoxyl sulfate (IS), while CKD-associated inflammation favors kynurenine pathway activation. Reduced kidney function promotes accumulation of IS and kynurenine metabolites. Experimental evidence suggests that these metabolites may contribute to oxidative stress, aryl hydrocarbon receptor (AhR) activation, blood–brain barrier (BBB) dysfunction, glial activation, and neuroinflammation. Human studies have identified associations between selected uremic toxins and depressive symptoms, but findings remain heterogeneous and do not establish causality. Depression in CKD is therefore depicted as a multifactorial clinical outcome influenced by biological, psychological, and disease-related factors. Potential therapeutic approaches include dietary and microbiome modulation, reduction of uremic toxin exposure, targeting of tryptophan metabolism, preservation of intestinal barrier integrity, and individualized psychiatric care.

Within this framework, tryptophan becomes a metabolic branching point. One pathway generates microbial indoles and ultimately IS; another generates kynurenine and neuroactive downstream metabolites; altered substrate distribution may additionally influence serotonin metabolism. These pathways may converge on oxidative stress, endothelial dysfunction, AhR signaling, BBB permeability, glial activation, neuroinflammation, and altered neurotransmission.

Depression in CKD nevertheless remains multifactorial. Psychosocial stress, socioeconomic factors, sleep disorders, anemia, vascular disease, medications, dialysis burden, physical inactivity, and comorbid illness remain important determinants. The microbiota–tryptophan–kidney–brain axis should therefore be viewed as a proposed biological framework contributing to susceptibility rather than a singular causal explanation.

9. Therapeutic Implications

The proposed axis suggests several potential intervention points. Dietary strategies that increase fermentable fiber may favor saccharolytic over proteolytic fermentation and enhance SCFA production. The dietary protein-to-fiber ratio has been associated with circulating IS and p-cresyl sulfate concentrations in CKD [25].

Prebiotics, probiotics, and synbiotics have consequently attracted interest. However, clinical evidence remains inconsistent. A systematic review found limited evidence that microbiome-directed supplementation consistently reduces circulating uremic toxins [26], and a randomized probiotic trial in hemodialysis did not demonstrate substantial reductions in inflammation or uremic toxins [27]. Conversely, a randomized study in nondialysis CKD reported that synbiotic supplementation modified gut microbial characteristics and reduced IS and inflammatory markers [28]. Differences in CKD stage, diet, microbial composition, intervention duration, and bacterial strains may partly explain these discrepancies.

Direct toxin reduction represents another strategy. The oral intestinal adsorbent AST-120 can reduce intestinal absorption of indole-derived precursors, but randomized clinical studies have not consistently demonstrated improvement in kidney outcomes [29]. Whether lowering IS or modifying tryptophan metabolism improves depressive symptoms remains largely unknown.

Targeting IDO/kynurenine metabolism, AhR signaling, intestinal permeability, or microbial tryptophan-metabolizing enzymes represents a more experimental strategy. Conventional psychiatric treatment remains essential. Nevertheless, the CAST randomized clinical trial found that sertraline did not significantly improve depressive symptoms compared with placebo among patients with nondialysis CKD and major depressive disorder [30]. This result does not imply that antidepressants are ineffective for all patients with CKD, but it illustrates the clinical heterogeneity of depression in this population.

Future therapeutic strategies may therefore require integrated management involving nephrology, gastroenterology, nutrition, and psychiatry rather than focusing exclusively on a single metabolite or pathway.

10. Conclusions and Future Perspectives

The microbiota–tryptophan–kidney–brain axis provides an integrative framework linking gastrointestinal dysbiosis, renal dysfunction, and depression. CKD reshapes intestinal microbial metabolism, disrupts barrier integrity, promotes systemic inflammation, and impairs clearance of biologically active metabolites. Tryptophan lies at the center of this network through serotonin, kynurenine, and microbial indole pathways.

Experimental evidence supports plausible effects of IS and kynurenine metabolites on oxidative stress, BBB integrity, glial activation, and neuroinflammation. Emerging longitudinal human data further associate selected gut-derived uremic toxins with depressive symptom burden, although findings across clinical settings remain heterogeneous and causality has not been established.

Future studies should move beyond isolated measurements of microbial composition or individual uremic toxins. Longitudinal studies integrating metagenomics, tryptophan metabolomics, free and total uremic toxin concentrations, inflammatory biomarkers, kidney function, dietary exposure, and standardized psychiatric phenotyping are needed. Such approaches may identify biologically distinct subgroups of depression in CKD and determine whether the microbiota–tryptophan–kidney–brain axis represents a modifiable therapeutic target.

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