Int J Clin Exp Physiol. 2026;13(1):50-51.
https://www.ijcep.org

Indoxyl Sulfate as an Emerging Biomarker and Pathogenic Mediator of Neurotoxicity in Chronic Kidney Disease

M Komagal*

Department of Physiology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), JIPMER Campus, Puducherry, INDIA.

Indoxyl Sulfate (IS) is a protein-bound uremic toxin that is synthesised during bacterial metabolism of dietary tryptophan by intestinal bacteria into indole. Indole is then metabolised into IS by the liver. In Chronic Kidney Disease (CKD), impaired renal excretion leads to the accumulation of IS. It has pro-inflammatory and pro-oxidant effects, leading to endothelial dysfunction and cardiovascular complications.[1]

Systematic reviews have shown IS to be toxic in vascular and renal disease.[2] It is an emerging biomarker and mediator in neurotoxicity.[3,4]

Pathophysiology of Neurotoxicity in CKD

Neurotoxicity in CKD is often described using the "kidney-brain axis." As renal function declines, brain function can become impaired due to the sequential accumulation, barrier-crossing, and central effects of uremic solutes such as IS.

Uremic toxin accumulation

As CKD progresses and functioning nephrons decrease, uremic solutes begin to accumulate. IS is continuously synthesised from indole derived from the gut.[1] It has high affinity for albumin, so it is poorly removed by haemodialysis.[5]

Only the free fraction of IS exerts biological effects, and therefore albumin binding must be considered when evaluating its toxicity.[2] Free IS levels remain inversely related to cognitive scores after adjusting for confounders in haemodialysis patients.[5] IS levels rise in both the serum and brain of CKD rodents.[3,6]

Blood-Brain Barrier (BBB) disruption

IS is an Aryl hydrocarbon Receptor (AhR) agonist on endothelial cells. In CKD rats, BBB permeability, measured by SPECT/CT imaging of a technetium-labelled tracer, was increased with renal impairment and correlated with serum IS and impaired cognition. AhR-knockout mice were protected from IS-induced barrier disruption and cognitive deficits, implicating AhR as a potential therapeutic target.[3] A disrupted BBB allows greater entry of neurotoxic solutes into the brain, compounding neurotoxicity.

Glial activation, oxidative stress, and neuroinflammation

Once IS enters the brain, it activates astrocytes and microglia. It increases reactive oxygen species and reduces Nrf2 and HO-1 expression, while promoting NF-κB activation and secretion of TNF-α and IL-6, causing neuronal cell death.[4] In CKD mice, this is accompanied by activation of the NLRP3 inflammasome in astrocytes and microglia, producing hippocampal inflammation and memory impairment.[6] IS also drives extrinsic apoptosis in differentiating neuronal cells in End-Stage Renal Disease (ESRD).[7]

Resulting cognitive and executive dysfunction

The above mechanisms culminate in measurable cognitive decline.IS levels correlate positively with impaired executive function in early CKD.[8] In haemodialysis patients, circulating free IS is inversely associated with Mini-Mental State Examination and Cognitive Abilities Screening Instrument scores,[5] and IS is similarly linked to impaired cognition in ESRD.[7]

Therapeutic significance & Diagnosis

Since IS is a gut-derived, albumin-bound toxin, interest has turned to reducing its production. AST-120, an oral carbon adsorbent that binds IS precursors in the gut, decreased IS levels in the serum and hippocampus, improving cognition in CKD mice.[6] However, patient-level benefit remains untested.[5,8] Serum IS levels correlate consistently with cognitive performance.[5,7,8] IS represents a promising biomarker for identifying patients at risk of neurological complications, supporting timely detection and management.

REFERENCES

1. Lano G, Burtey S, Sallée M. Indoxyl sulfate, a uremic endotheliotoxin. Toxins (Basel). 2020;12(4):229. doi: 10.3390/toxins12040229. PMID: 32260489.
2. Vanholder R, Schepers E, Pletinck A, Nagler EV, Glorieux G. The uremic toxicity of indoxyl sulfate and p-cresyl sulfate. J Am Soc Nephrol. 2014;25(9):1897-907. doi: 10.1681/ASN.2013101062. PMID: 24812165.
3. Bobot M, Thomas L, Moyon A, Fernandez S, McKay N, Balasse L, *et al.* Uremic toxic blood-brain barrier disruption mediated by AhR activation leads to cognitive impairment during experimental renal dysfunction. J Am Soc Nephrol. 2020;31(7):1509-21. doi: 10.1681/ASN.2019070728. PMID: 32527975.

DOI: 10.5530/ijcep.2026.13.1.7

Copyright Information :
Copyright Author (s) 2026 Distributed under Creative Commons CC-BY 4.0

Publishing Partner : Manuscript Technomedia. [www.mstechnomedia.com]

www.ijcep.org

4. Adesso S, Magnus T, Cuzzocrea S, Campolo M, Rissiek B, Paciello O, *et al.* Indoxyl Sulfate Affects Glial Function, Increasing Oxidative Stress and Neuroinflammation in Chronic Kidney Disease: Interaction between Astrocytes and Microglia. Front Pharmacol. 2017;8:370. doi: 10.3389/fphar.2017.00370. PMID: 28659803.
5. Lin YT, Wu PH, Liang SS, Mubanga M, Yang YH, Hsu YL, *et al.* Protein-bound uremic toxins are associated with cognitive function among patients undergoing maintenance hemodialysis. Sci Rep. 2019;9(1):20388. doi: 10.1038/s41598-019-57004-7. PMID: 31892730.
6. Li LC, Chen WY, Chen JB, Lee WC, Chang CC, Tzeng HT, *et al.* The AST-120 recovers uremic toxin-induced cognitive deficit via the NLRP3 inflammasome pathway in astrocytes and microglia. Biomedicines. 2021;9(9):1252. doi: 10.3390/biomedicines9091252. PMID: 34572437.
7. Hsieh CC, Lu KC, Huang CL, Wang JJ, Yeh TY, Lin SM, *et al.* Indoxyl sulfate is associated with cognitive impairment in ESRD patients by activating extrinsic apoptosis in neuronal cells during the differentiation process. Int J Med Sci. 2025;22(8):1736-49. doi: 10.7150/ijms.109245. PMID: 40225859.
8. Yeh YC, Huang MF, Liang SS, Hwang SJ, Tsai JC, Liu TL, *et al.* Indoxyl sulfate, not p-cresyl sulfate, is associated with cognitive impairment in early-stage chronic kidney disease. Neurotoxicology. 2016;53:148-52. doi: 10.1016/j.neuro.2016.01.006. PMID: 26797588.

Correspondence:
Ms. M Komagal
Department of Physiology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), JIPMER Campus, Puducherry-605006, INDIA.
Email: mkomagal@gmail.com

Received: 06-03-2026;
Revised: 07-04-2026;
Accepted: 09-04-2026.

Cite this article: Komagal M. Indoxyl Sulfate as an Emerging Biomarker and Pathogenic Mediator of Neurotoxicity in Chronic Kidney Disease. Int J Clin Exp Physiol. 2026;13(1):50-51.

www.ijcep.org