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Letter to Editor

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Melatonin: A potential therapeutic approach for neuropathic pain in patients with dialysis-dependent chronic kidney disease

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Neuropathic pain is a common and debilitating complication in patients with end-stage kidney disease (ESKD) undergoing dialysis, with conventional treatments often limited by adverse effects and poor tolerability in this population due to altered pharmacokinetics.[1,2] This letter evaluates the therapeutic potential of melatonin, a neuroprotective agent with antioxidant and anti-inflammatory properties, for managing neuropathic pain in patients with dialysis-dependent chronic kidney disease (CKD), while highlighting evidence gaps.[3]

We performed a narrative literature search using PubMed, Scopus, and Web of Science databases up to September 2025. Keywords included "melatonin", "neuropathic pain", "dialysis", and "chronic kidney disease". Eligible studies encompassed experimental and clinical research addressing melatonin's effects on neuropathic pain and safety in dialysis-relevant populations. Both preclinical and clinical data were considered to provide a comprehensive view.

Neuropathic Pain in CKD: Clinical Challenge

Peripheral and autonomic neuropathies, such as uremic polyneuropathy and mononeuropathies, are highly prevalent in CKD population and contribute to functional disability.[4] Neuropathic pain management is particularly challenging, as conventional agents including tricyclic antidepressants, gabapentinoids, and serotonin-norepinephrine reuptake inhibitors (SNRIs) often cause adverse effects or are poorly tolerated, partly due to altered pharmacokinetics in CKD.

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Table 1. Clinical trials assessing melatonin efficacy in neuropathy and confirming its safety in patients with dialysis-dependent chronic kidney disease (CKD)

Authors	Population	Design	Melatonin dose	Main outcomes	CKD/neuropathy relevance
Ostadmohammadi et al.[11]	Diabetic hemodialysis patients	RCT, placebo-controlled	10 mg/day	Improved metabolic parameters, well-tolerated with no major adverse effects	Indirect dialysis-CKD population evidence, safety confirmation
Edalat-Nejad et al.[12]	Hemodialysis patients	Randomized, double-blind crossover clinical trial	3 mg/day	Improved sleep quality, decreased EPO requirement, increased HDL cholesterol	Indirect dialysis-CKD population evidence
Gilron et al.[13]	Chronic peripheral neuropathic pain	RCT, placebo-controlled	3 to 12 mg titrated	No significant reduction in neuropathic pain intensity compared to placebo	Contradictory clinical evidence on analgesic efficacy
Kheshti et al.[15]	Cancer chemotherapy patients	RCT, double-blind	20 mg/day	Significant reduction in chemotherapy-induced neuropathy severity and improved quality of life	Clinical neuropathy evidence
Jafari et al.[16]	Hemodialysis-CKD patients	RCT, placebo-controlled	3 mg/day	Improved cognition function and sleep quality	Indirect dialysis-CKD population evidence

CKD: Chronic kidney disease; RCT: Randomized controlled trial; HDL: High-density lipoprotein; EPO: Erythropoietin

Therefore, alternative and safer therapies are urgently needed.[5]

Melatonin Mechanisms Relevant to Neuropathy

Melatonin exerts neuroprotective effects by binding to melatonin 2 (MT2) receptors, suppressing apoptosis, and inhibiting inflammatory signaling pathways such as the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)/ nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3 (NLRP3) inflammasome. These actions suggest its capability to modulate neuropathic pain pathogenesis effectively.[3]

Pharmacokinetics and Safety Considerations in CKD

Melatonin is primarily metabolized hepatically via the enzyme cytochrome P450 1A2 (CYP1A2), with renal excretion of its metabolites. CKD can alter melatonin metabolism and clearance, potentially leading to its accumulation or altered metabolite profiles. In the general population, melatonin is well tolerated, with mild adverse effects such as drowsiness and headache. However, patients with CKD require close monitoring due to impaired renal function, possible modulation of immune responses, and effects on sleep architecture. Co-administration with central nervous system (CNS) depressants demands particular caution, especially in elderly individuals, to avoid excessive sedation, drowsiness, dizziness, headache, and confusion.[6-8]

Evidence from Experimental and Clinical Studies

Several preclinical and clinical investigations have demonstrated melatonin's beneficial effects in various neuropathic models, including diabetic neuropathy and viral and chemotherapy-induced neuropathies.[9,10] Although research specific to CKD populations remains limited, emerging studies have confirmed melatonin's safety and potential advantages in patients undergoing hemodialysis[11-14] (Table 1). In chemotherapy-induced neuropathy, a double-blind randomized controlled trial (RCT) showed that melatonin at 20 mg/day significantly reduced neuropathy severity and improved quality of life (QOL) in patients with cancer receiving oxaliplatin-based regimens.[15] In diabetic hemodialysis patients, 10 mg/day melatonin improved metabolic parameters and was well tolerated, with no significant adverse effects reported.[11] Similarly, 3 mg/day melatonin enhanced cognitive function and sleep quality in hemodialysis patients.[16] Another trial in hemodialysis patients found that 3 mg/day melatonin improved sleep, reduced erythropoietin (EPO) requirements, and increased high-density lipoprotein (HDL) cholesterol levels.[12] Contrasting these findings, a recent double-blind, placebo-controlled crossover RCT in patients with chronic peripheral neuropathic pain (titrated doses of 3-12 mg/day) reported no significant reduction in pain intensity compared to

placebo, highlighting conflicting evidence on melatonin's analgesic efficacy.[13]

Future Directions: Given its favorable safety profile and neuroprotective properties, melatonin represents a promising candidate for neuropathic pain management in patients with dialysis-dependent CKD. Well-designed, adequately powered RCTs specifically targeting uremic neuropathic pain are needed to clarify efficacy, optimal dosing, and impacts on pain intensity and QOL. Including this promising strategy in your journal will encourage focused research in this challenging domain, potentially improving therapeutic options for neuropathic pain in CKD.

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Conflict of Interests

The authors declare no conflict of interest in this study.

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