The Role of Serum Potassium in Uremic Peripheral Neuropathy: A comparative study between CKD stage 3-4 and stage 5

Elda CULE
Department of Nephrology, Hygeia Hospital Tirana, Albania

Merita RROJI
Department of Nephrology, University Hospital Center "Mother Teresa", Tirana, Albania

Abstract

Background and objectives: Uremic peripheral neuropathy (UPN) is a frequent and disabling complication of chronic kidney disease (CKD), particularly in its advanced stages. The condition arises through multiple mechanisms, including the accumulation of uremic toxins, oxidative stress, and metabolic derangements. However, the contribution of electrolyte imbalances, especially disturbances in serum potassium, has received comparatively little attention. Hyperkalemia is common in CKD, and experimental data suggest that elevated extracellular potassium may depolarize axons and exacerbate neuropathic dysfunction. This study aimed to explore the relationship between serum potassium levels and neuropathy severity in patients with moderate-to-advanced CKD.

Methods: This is a cross-sectional analysis of 63 non-diabetic adults with confirmed CKD, of whom 57% were in stages 3–4 and 33% in stage 5 (non-dialysis). Peripheral neuropathy was defined according to established literature as an MNSI score greater than seven and/or abnormal findings on nerve conduction studies (NCS), consistent

with diagnostic thresholds used in prior epidemiological and clinical studies of CKD-related neuropathy. Neuropathy assessment was conducted within 24 hours of serum potassium measurement. Descriptive statistics, group comparisons, correlation testing, and multivariate regression analyses were applied.

Results: The mean age of participants was 65.1 years; 33% females. UPN was more prevalent and severe in stage 5 patients, with 63% recording an MNSI score >7 compared with 27% of those in stages 3–4 ($p<0.001$). Serum potassium levels were significantly higher in stage 5 patients compared with those in stages 3–4 (5.1 ± 0.6 vs. 4.75 ± 0.5 mmol/L, $p=0.026$). A moderate positive correlation was found between serum potassium levels and MNSI scores ($r = 0.48$, $p <0.03$). Multivariate regression analysis demonstrated that both potassium ($\beta = +0.87$, $p = 0.013$) and eGFR ($\beta = -0.02$, $p = 0.049$) were independent predictors of neuropathy severity, together accounting for 32% of the observed variance ($R^2 = 0.32$).

Conclusion: Elevated serum potassium is independently associated with increased severity of UPN in CKD, especially in stage 5 disease. The observed relationship supports experimental evidence connecting hyperkalemia to axonal depolarization and indicates that potassium imbalance may accelerate neuropathic changes even in earlier CKD stages. These findings highlight the importance of vigilant potassium monitoring and early correction of abnormalities as potentially modifiable strategies to slow neuropathy progression and enhance patient quality of life.

***Keywords**: chronic kidney disease, uremic neuropathy, serum potassium, hyperkalemia, Michigan Neuropathy Screening Instrument, CKD stages.*

Introduction

Neurological complications of chronic kidney disease involve both the central and peripheral nervous systems. Uremic peripheral neuropathy is associated with a high prevalence of up to 90% of advanced CKD patients, presenting as distal sensory loss, pain, paraesthesia, and weakness primarily in lower limbs (Arnold et al., 2013). Polyneuropathy, mononeuropathies, cranial neuropathies, autonomic neuropathy, ischemic neuropathy, and uremic myopathy are among the peripheral nervous system illnesses that considerably lower patients' quality of life and raise their risk of cardiovascular problems. It develops as a result of uremic toxin buildup and progressive loss of renal function, although it may also be impacted by concomitant disorders, including autoimmune diseases, hypertension, and diabetes mellitus. Peripheral nerve injury, both structural and functional, causes a wide range of sensory, motor, and autonomic abnormalities (Arnold et al., 2017). Autonomic traits such as gastrointestinal dysmotility, orthostatic hypotension, and sexual dysfunction may further complicate the clinical picture. (Arnold et

al., 2017) Table 1 illustrates how the various consequences of uremic peripheral neuropathy are reflected in its clinical symptoms.

TABLE 1. Subtypes of PUN and clinical manifestation.

Subtypes of uremic peripheral neuropathy (UPN)	Clinical features
Uremic polyneuropathy	Paresthesia ("stocking-and-glove" pattern), burning pain, muscle weakness, loss of reflexes, impaired vibration and position sense
Autonomic neuropathy	Impotence, bladder and bowel dysfunction, sweating abnormalities,
	orthostatic hypotension, increased risk of arrhythmias and sudden cardiac death
Mononeuropathies (carpal tunnel syndrome, ulnar or femoral neuropathy)	Pain, numbness, weakness, and atrophy of muscles innervated by the affected nerve; in carpal tunnel syndrome, symptoms often worsen during dialysis
Cranial neuropathies	Hearing impairment (up to deafness), vertigo, impaired odour discrimination, rarely visual disturbances and facial nerve palsy
Ischemic neuropathy (after creation of arteriovenous fistula)	Acute/subacute sensory and motor deficits in the limb, steal syndrome, skin ulcers
Uremic myopathy	Proximal muscle weakness (especially in the legs), exercise intolerance, muscle atrophy, easy fatigability

Pathogenesis of peripheral uremic neuropathy in CKD and the role of potassium disturbances across CKD stages

Uremic toxin accumulation, metabolic disorders (including acidosis, hyperkalaemia, and calcium-phosphate imbalance), secondary hyperparathyroidism, anaemia resulting from iron and erythropoietin deficiency, vitamin deficiencies (B1, B6, and B12, D), malnutrition, ischemia, and hypoxia of nervous structures are all part of the multifactorial pathogenesis. Although traditionally attributed to uremic toxin retention, increasing evidence highlights the modifying role of electrolyte derangements, particularly hyperkalaemia, in accelerating neuropathic progression before initiation of dialysis. Hyperkalaemia contributes strongly to uremic neuropathy by causing dose- dependent nerve dysfunction, which can be mitigated through potassium restriction. (Vanholder et al., 2028) Declining glomerular filtration rate (GFR) in CKD leads to elevated concentration of middle molecules and protein-bound uremic toxins, including indoxyl sulphate, p-cresyl sulphate, and guanidino compounds, B2-microglobulin, and advanced glycation end-products. (Niwa, 2010, Duranton et al.,2012) These compounds exert neurotoxic effects through several mechanisms: inhibition of Na-K ATPase, disruption of calcium homeostasis, mitochondrial dysfunction, impaired axonal

transport, and induction of oxidative stress. Histopathological studies consistently demonstrate distal axonal loss, pre-nodal injury, and demyelination secondary to metabolic derangements and microvascular dysfunction. (Bolton, 1980, Krishnan, 2009)

Contribution of hyperkalaemia to nerve conduction abnormalities

Potassium plays a crucial role in determining neural resting membrane potential. In CKD stages 4-5, chronic or intermittent hyperkalaemia becomes increasingly prevalent due to impaired renal excretion, metabolic acidosis, and use of the renin-angiotensin- aldosterone system inhibitors, and hyporeninemic hypoaldosteronism. (Kovesdy, 2014) Elevated extracellular potassium reduces the resting membrane gradient, resulting in atrial depolarisation of the peripheral axons. This leads to slowed nerve conduction failure, particularly in already compromised axons. (Krishnan et al., 2003; Kiernan & Kaji 2003; Hyperkalaemia alone does not induce structural neuropathy, but exacerbates functional deficits caused by uremic toxins. Studies demonstrate that higher serum potassium levels correlate with greater abnormalities on nerve conductions studies (NCS), including reduced sensory nerve action potential (SNAP) amplitudes and prolonged motor distal latencies, even after adjusting for estimated GFR. The combination of chronic metabolic acidosis and hyperkalaemia further impairs Na-K ATPase activity, amplifying excitability disturbances in peripheral nerves.

Progression across CKD stages in pre-dialysis.

In CKD stage 3, neuropathic changes are generally subclinical, with minimal slowing of conduction velocities and rare electrolyte abnormalities. As patients progress to stage 4, the accumulation of uremic solutes intensifies, and intermittent hyperkalaemia becomes more frequent. Clinical manifestations often emerge during this stage and show a measurable association with rising serum potassium levels. (Aggwaral et al., 2013) In stage 5, pre-dialysis, persistent hyperkalaemia, metabolic acidosis synergistically impair axonal membrane function. Electrophysiological studies at this stage typically reveal a significant reduction in SNAP and CMAP amplitudes of both motor and sensory conduction velocities, reflecting advanced axonal degeneration. The patients in advanced pre-dialysis stages exhibit more neuropathic findings in both clinical scoring systems (e.g., MNSI, TNS) and electrodiagnostic evaluation (e.g., ENMG, NCS). (Stompor et al., 2019). Table 2 summarises the mechanism of high potassium levels and its impact in CKD.

TABLE 2. Summarise the effect of high potassium in different stages of CKD

Mechanism	Effect of High Potassium (Hyperkalaemia)	Impact in Chronic Kidney Disease (CKD)
Reduced Na^+/K^+-ATPase activity due to uremic toxins	Depolarisation of neuronal membrane; impaired repolarization	Worsens axonal dysfunction, especially in CKD stage 4–5
Elevated extracellular potassium concentration	Inactivation of voltage- gated sodium channels → conduction slowing	Reduced sensory and motor nerve conduction velocities (ENMG abnormalities)
Metabolic acidosis and aldosterone deficiency	Further retention of potassium, persistent hyperkalaemia	Earlier clinical neuropathy: paresthesia, numbness, muscle weakness
Axonal vulnerability due to accumulated uremic toxins	Hyperkalaemia exacerbates conduction block in damaged axons	More severe neuropathy in Pre-dialysis CKD (4–5)
Retention of protein-bound toxins (indoxyl sulphate, p-cresyl sulphate)	Synergistic worsening of membrane excitability defects	Strong association with abnormal NCS findings and higher neuropathy scores

Purpose of the study

This study aims to explore the association of high potassium levels with neuropathy severity in patients with moderate-to-advanced chronic kidney disease (CKD).

Methods Study design

This was a cross-sectional observational study designed to evaluate the relationship between serum potassium levels and peripheral neuropathy in adults with chronic kidney disease (CKD). All assessments, including biochemical measurements and neuropathological evaluations, were performed within a standardised timeframe to minimise measurement variability.

Participants

A total of 63 non-diabetic adults with CKD were enrolled. Eligibility criteria included age≥18 years, confirmed diagnosis of CKD stages 3–5 (not yet on dialysis), and absence of known causes of neuropathy other than uremia. Exclusion criteria included diabetes mellitus, alcohol misuse, active infection, neurological disorders, or use of neurotoxic medications. The distribution of CKD stages was as follows:

- 57% in CKD stages 3–4
- 33% in CKD stage 5 (pre-dialysis)
- 87% receiving ACE inhibitors or angiotensin receptor blockers (ARB)

Neuropathy Screening Instruments

Peripheral neuropathy was assessed using two complementary methods:

1. Michigan Neuropathy Screening Instrument (MNSI): A structured clinical and physical examination evaluating foot appearance, ulceration, ankle reflexes, and vibration sensation in combination with a questionnaire and a score greater than 7 indicated neuropathy.
2. Nerve Conduction Studies (NCS): Standardised electrophysiological testing measured sensory and motor nerve conduction velocities, amplitudes, and latencies. Abnormal results were defined using established reference ranges and interpreted by a neurologist blinded to biochemical values.

Timing of assessments

Neuropathy evaluation (MNSI) was performed within 24 hours of serum potassium measurement to ensure temporal consistency between electrolyte status and neurophysiological findings.

Data collection and variables

Collected variables included demographic data, CKD stage, medication use (ACE-i/ARB), serum potassium concentration, and neuropathy outcomes (MNSI score parameters). Serum potassium was analysed both as a continuous variable and as a categorical variable (normokalaemia vs. hyperkalaemia).

Statistical analysis

Descriptive statistics were used to summarise demographic and clinical characteristics. Associations between serum potassium and neuropathy were evaluated using correlation analyses (Pearson or Spearman), group comparison tests (t-test or Mann– Whitney U), and multivariate linear regression to determine whether serum potassium independently predicted neuropathy severity after adjusting for CKD stage and other covariates. A significance level of $p > 0.05$ was considered statistically significant.

Results

The study population consisted of older adults with chronic kidney disease (CKD), with a mean age of 65.1 years and a female proportion of 33%. The prevalence of uremic neuropathy (UNP), defined as an MNSI score ≥7, differed

substantially across CKD stages. Patients in stage 5 demonstrated a significantly higher prevalence of neuropathy (63%) compared with those in stages 3–4 (27%). This gradient indicates a strong association between declining kidney function and worsening neuropathic burden.

Serum potassium levels also showed a clear stage-dependent pattern. Participants in stage 5 exhibited higher mean potassium concentrations (5.1 ± 0.6 mmol/L), whereas those in stages 3-4 demonstrated lower levels (4.7 ± 0.5 mmol/L). These findings reflect the expected physiological rise in potassium with advancing CKD due to impaired renal potassium excretion.

The analysis (Figure 1) demonstrates a positive relationship between serum potassium levels and MNSI scores, with the highest neuropathy severity observed in CKD stage 5. The figure shows both a higher median MNSI score and a wider distribution of scores in stage 5 patients, suggesting increased severity and greater variability in neuropathic involvement. The statistical comparison (p >0.001) confirms that neuropathy severity differs significantly by CKD stage, supporting the hypothesis that hyperkalaemia exacerbates nerve dysfunction.

Overall, these findings suggest that elevated potassium levels may act as an amplifying factor for neuropathy in advanced CKD. While uremic toxin accumulation remains a primary driver of axonal injury, the strong correlation between potassium concentration and MNSI scores highlights a potential interaction between electrolyte imbalance and neuronal membrane excitability. These results reinforce the importance of close potassium monitoring in pre-dialysis CKD patients to help anticipate and mitigate neurologic complications.

Serum potassium levels were significantly higher in patients with stage 5 CKD compared with those in stages 3–4 (5.1 ± 0.6 vs 4.7 ± 0.5 mmol/L; p = 0.026). As illustrated in Figure 2, potassium values in stage 5 showed an upward shift and greater variability, consistent with impaired renal potassium handling in advanced CKD.

FIGURE 1

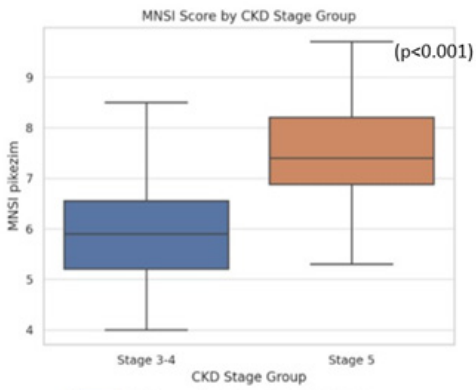
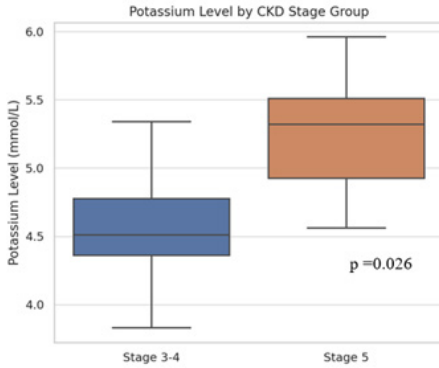
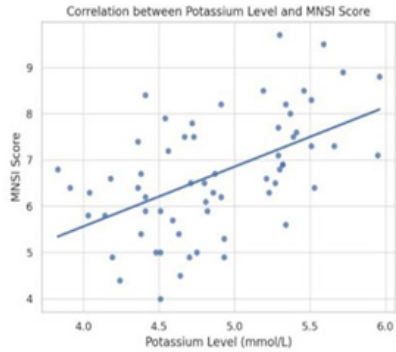


FIGURE 2. Correlation between potassium levels and CKD stage



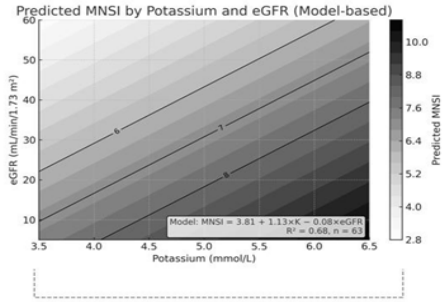
Using Pearson correlation, serum potassium correlated moderately and positively with MNSI (r = 0.48; p = 0.03) as illustrated in figure 3.

FIGURE 3. Correlation between MNSI and potassium levels



In multivariable linear regression, higher serum potassium was associated with greater neuropathy severity (β = 0.87 MNSI points per 1 mmol/L increase, p = 0.013), while lower kidney function was also associated with greater severity (β = −0.02 MNSI points per 1 mL/min/1.73 m² decrease in eGFR, p = 0.049). Together, potassium and eGFR explained 32% of the variance in MNSI (R^2 = 0.32). Figure 4.

FIGURE 4. Multivariate linear regression



Discussion

In this cross-sectional study of non-diabetic adults with chronic kidney disease (CKD), we observed a clear stage-dependent increase in both serum potassium levels and the prevalence of uremic peripheral neuropathy. Patients with stage 5 CKD exhibited significantly higher potassium concentrations and higher Michigan Neuropathy Screening Instrument (MNSI) scores compared with those in stages 3–4, suggesting that worsening kidney function contributes directly to both electrolyte imbalance and neurophysiologic deterioration. The association between hyperkalaemia and neuropathy severity is biologically plausible. Declining renal function reduces potassium excretion and increases the burden of uremic toxins, both of which impair neuronal membrane stability. Elevated extracellular potassium has been shown to cause partial membrane depolarisation, impaired repolarisation, and inactivation of voltage-gated sodium channels, leading to slowed nerve conduction and reduced action potential amplitude. These electrophysiologic alterations may amplify underlying axonal injury caused by uremic toxins. Our findings are consistent with this mechanistic framework, as patients with higher potassium levels demonstrated more severe neuropathic manifestations. Another important observation is the greater variability in potassium levels among stage 5 participants. This heterogeneity may reflect differences in dietary intake, RAAS inhibitor use, metabolic acidosis, or tubular dysfunction. Regardless of the underlying cause, such variability underscores the need for closer biochemical monitoring in the pre-dialysis population. The strong correlation between potassium concentration and MNSI score in our cohort raises the possibility that early correction of hyperkalaemia may mitigate progression of neuropathy; however, causality cannot be inferred from cross- sectional data. Strengths of this study include the combined use of clinical (MNSI) and electrophysiologic (NCS) assessments, and the narrow time interval between potassium measurement and neuropathy evaluation. Limitations include the modest sample size, the cross-sectional design, and the lack of quantification of specific uremic toxins, which could provide deeper mechanistic insight. Despite these limitations, our findings contribute to growing evidence that electrolyte abnormalities—particularly hyperkalaemia—may play a clinically meaningful role in worsening peripheral neuropathy in advanced CKD.

Conclusion

Serum potassium levels and neuropathy severity both increased with advancing CKD stage. Patients with stage 5 CKD demonstrated significantly higher potassium concentrations and a greater burden of uremic peripheral neuropathy compared

with those in stages 3–4. These findings highlight hyperkalaemia as a potential amplifying factor for neuropathic dysfunction in the pre-dialysis population. Early identification and management of potassium abnormalities may represent an important strategy to mitigate neurologic complications. Longitudinal studies are needed to assess causality and to determine whether potassium-lowering interventions can slow the progression of uremic neuropathy.

References

1. Aggarwal HK, Sood S, Jain D, et al. Evaluation of the spectrum of peripheral neuropathy in predialysis patients with chronic kidney disease. Ren Fail. 2013; 35(10): 1323–1329, doi: 10.3109/0886022X.2013.828261, indexed in Pubmed: 23964701.
2. Aggarwal, A., Kumar, V., Sakhuja, V., Kohli, H. S., Gupta, K. L., & Jha, V. (2013). Association of serum potassium with nerve conduction velocity in patients with chronic kidney disease.*Nephrology, 18*(9), 609–615.
3. Arnold R, Issar T, Krishnan AV, Pussell BA. Neurological complications in chronic kidney disease. JRSM Cardiovasc Dis. 2016 Nov 3;5:2048004016677687. doi: 10.1177/2048004016677687. PMID: 27867500; PMCID: PMC5102165.
4. Arnold R, Pianta TJ, Pussell BA, Kirby A, O'Brien K, Sullivan K, Holyday M, Cormack C, Kiernan MC, Krishnan AV. Randomised, Controlled Trial of the Effect of Dietary Potassium Restriction on Nerve Function in CKD. Clin J Am Soc Nephrol. 2017 Oct 6;12(10):1569-1577. doi: 10.2215/CJN.00670117. Epub 2017 Sep 11. PMID: 28893921; PMCID: PMC5628705.
5. Bolton, C. F. (1980). Peripheral neuropathies in chronic renal failure. Canadian Journal of Neurological Sciences, 7*(2), 89–96.
6. Duranton, F., Cohen, G., De Smet, R., et al. (2012). Normal and pathologic concentrations of uremic toxins. *Journal of the American Society of Nephrology, 23*(7), 1258–1270.
7. Krishnan, A. V., & Kiernan, M. C. (2009). Neurological complications of chronic kidney disease. *Nature Reviews Neurology, 5*(10), 542–551.
8. Krishnan, A. V., Phoon, R. K., Pussell, B. A., Charlesworth, J. A., & Kiernan,

M. C. (2005). Altered nerve excitability properties in chronic renal failure indicate membrane depolarisation due to hyperkalemia. *Brain, 128*(10), 2361–2370. Kovesdy, C. P. (2014). Management of hyperkalemia in chronic kidney disease.

9. Nature Reviews Nephrology, 10*(11), 653–662.
10. Kiernan, M. C., & Kaji, R. (2003). Physiological basis of nerve conduction abnormalities in hyperkalemia. *Clinical Neurophysiology, 114*(7), 1321–1328.
11. Niwa, T. (2010). Uremic toxicity of indoxyl sulfate. *Nagoya Journal of Medical Science, 72*(1–2), 1–11.
12. Stompór, T., Perkowska-Ptasinska, A., Szczepanska, M., et al. (2019). Early clinical and electrophysiological markers of uremic neuropathy in predialysis CKD patients. Renal Failure, 41*(1), 772–781.