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Original Article

Evaluating the Association of Hyperuricemia in End-Stage Renal Disease Patients on Hemodialysis at a Tertiary Care Hospital

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ABSTRACT

Objective: To highlight the association of hyperuricemia in patients of Chronic Kidney Disease stage 5 on Hemodialysis (CKD-5D) at a tertiary care hospital.

Study Design: Cross-sectional study.

Place and Duration of Study: Department of Nephrology and Dialysis Unit, Pak Emirates Military Hospital, Rawalpindi Pakistan, from Jul to Dec 2021.

Methodology: Using a consecutive sampling technique, CKD patients of either gender with age >15 years, both dialysis dependent (CKD-5D) and non-dialysis dependent (CKD-5ND), were included and divided into two groups of 80 each. Serum uric acid levels of both groups (CKD-5ND and CKD-5D) patients were assessed and analyzed. Measures of association odds ratio and the prevalence ratio, were calculated.

Results: The mean age was 53.76±18.26 years in Group-A (CKD-5ND) and 52.46±17.50 years in Group-B (CKD-5D) (p=0.667). Out of the total 80 CKD-5D patients in Group-B, 14(17.5%) underwent HD once weekly, 37(46.3%) twice weekly, and 29(36.3%) undergoing hemodialysis thrice weekly. CKD-5ND patients tend to have higher levels of uric acid as compared to CKD-5D patients, 51(63.8%) vs 33(41.3%), respectively (p=0.004). Patients undergoing once weekly hemodialysis had higher levels of uric acid, 9(27.3%), and patients undergoing twice or thrice weekly hemodialysis, 17(51.5%) and 7(21.2%), had hyperuricemia, respectively (p=0.032).

Conclusion. There is a high prevalence of hyperuricemia in CKD patients, and with declining eGFR, uric acid levels increase. Patients undergoing thrice weekly maintenance hemodialysis had a lower prevalence of raised uric acid levels with once weekly hemodialysis and CKD patients without hemodialysis.

Keywords: Chronic Kidney Disease, Glomerular Filtration Rate, Hemodialysis, Hyperuricemia, Peritoneal Dialysis, Renal Replacement Therapy, Uric Acid.

How to Cite This Article: *Ansar M, Raja KM, Saeed HA, Hammad M, Alvi FN, Abidin Z. Evaluating the Association of Hyperuricemia in End-Stage Renal Disease Patients on Hemodialysis at a Tertiary Care Hospital. Pak Armed Forces Med J 2025; 75(4): 650-654.*
DOI: https://doi.org/10.51253/pafmj.v75i4.9450

INTRODUCTION

Chronic kidney disease (CKD) has become a prominent health concern worldwide with projected prevalence of 13.4% and patients with stage 5 disease (glomerular filtration rate (GFR) <15 ml/min/1.73m^2) needing hemodialysis (CKD-5D) are estimated between 4.9-7.1 million.[1] The approximated global burden of disease showed that there were 1.4 million deaths from CKD in 2019, which is 20% higher than in 2010.[2] Uric acid is the end product of purine nucleotide metabolism in the body, which is excreted from the body through the kidneys via the urate transporter.[3] The kidneys are responsible for the excretion of around 2/3rd (60-70%) of uric acid, the gastrointestinal tract being responsible for the rest (30-40%).[3] Hyperuricemia is prevalent in 40-60% of CKD patients of stage 1-3 and 70% of CKD stage 4 or 5.[4] The contributing factors in the emergence of hyperuricemia in kidney failure include diminished urate filtration resulting from decreased GFR, reduced urate tubular secretion due to tubulointerstitial disease, and management with diuretics.[4]

The prevalence of hyperuricemia (serum urate level >405 µmol/L (>6.8 mg/dl) escalates with reducing eGFR and disease stage, affecting 70% of CKD stage 4 or 5 patients.[5] There is an association of CKD and hyperuricemia, which amplifies the inflammatory process, oxidative stress, and endothelial damage, leading to the development and worsening of cardiovascular damage. Hence, increased serum urate levels are consistently accompanied by an increased risk of death in the general population as well as non-dialysis dependent CKD, in contrast to dialysis

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Received: 03 Nov 2022; revision received: 20 Apr 2023; accepted: 16 May 2023

dependent CKD, who tend to have a lower prevalence of hyperuricemia.[6] The study and literature related to effect of hyperuricemia in CKD-5 showed that there is a link between higher uric acid levels and lower all-cause mortality, with no significant association with cardiovascular mortality.[7] In studies, it has been demonstrated that there is an inverse relationship between GFR and serum urate levels. Also, asymptomatic hyperuricemia is labeled as a risk factor for declining eGFR in CKD patients.[8] Available data support that higher serum uric acid levels have a damaging impact on renal function, leading to declining eGFR and negatively impacting the stage of CKD and leading to advanced kidney disease.[9] Uric acid has complex relationships with morbidity and mortality in patients with CKD-5D. In patients with standard hemodialysis prescription, a high-flux dialyzer can remove almost 70% of uric acid, which is comparatively even higher in case of peritoneal dialysis.[10]

This study aimed to assess the association of hyperuricemia in the background of chronic kidney disease in patients of CKD-5D in comparison to non-dialysis CKD-5 patients. The long-term association of hyperuricemia with hemodialysis has not been studied well in our part of the world. This study was designed to generate data from our dialysis population in the context of hyperuricemia.

METHODOLOGY

It was conducted as a cross-sectional study at the Nephrology Department and Dialysis Unit of Pak Emirates Military Hospital, Rawalpindi Pakistan, from Jul to Dec 2021, following approval of the Ethical Committee of PEMH (EC: A/28/188(1). Sample size was calculated using online WHO sample size calculator, keeping in view the estimated population of End Stage Renal Disease (ESRD) in CKD requiring hemodialysis to be 3 million, among a 13.4% prevalence of ESRD in CKD.[11] A total of 160 patients were sampled using a consecutive non-probability sampling technique.

Inclusion Criteria: All consented patients of either gender, age >15 years with CKD-5 (eGFR <15mL/min/1.73m^2), both on hemodialysis for at least 1 year and without hemodialysis dependency were included in the study.

Exclusion Criteria: All those patients who had a previous history of gout, were receiving urate-lowering therapy, or were on peritoneal dialysis, BMI >25, or had any tumor or malignancy were excluded from the study.

All patients of CKD-5 diagnosed for at least 1 year, visiting the outpatient department or Dialysis unit of PEMH, were included in the study after thorough informed consent. A total of 160 CKD-5 patients presenting to PEMH during the study period were divided into two groups of 80 each. Group-A consisted of CKD-5 patients without dialysis dependency (CKD-5ND), and Group-B had CKD-5 patients on hemodialysis (CKD-5D) for at least 1 year. All patients were advised serum uric acid levels, followed up, and data were collected after lab results. Patient's age, gender, duration of CKD, and the cause of CKD were assessed. Moreover, the duration of hemodialysis as renal replacement therapy studied in this study, along with weekly hemodialysis dependency, adequacy, and compliance with hemodialysis, were also noticed in the study as a contributing factor.

Association of hyperuricemia in CKD-5 patients was observed and compared between dialysis-dependent (CKD-5D) and non-dialysis patients (CKD-5ND) with measures of association including Odds ratio (OR) and prevalence ratio (PR). The routine diet of the patients was also inquired about by a thorough history from patients as well as their attendants, as high protein intake contributes to affecting serum uric acid levels. A high protein diet was defined as a diet in which 20% to 30% of daily calories came from protein sources or taking > 150 gm protein/day.

The data were summarized as mean, frequency, and percentage, and then analyzed. Odds ratio and prevalence ratio were also assessed, and the Pearson Chi-square statistical test and independent sample t test were used for analysis. The p-value of ≤0.05 was regarded as statistically significant.

RESULTS

Among 160 enrolled patients, the mean age was 53.76±18.26 years in Group-A and 52.46±17.50 years in Group-B patients (p=0.667). There were 46(57.5%) males and 34(42.5%) females with CKD-5ND in the Group-A and 38(47.5%) males and 42(52.5%) female patients of CKD-5D in Group-B (p=0.184). The underlying cause of CKD was also inquired, and Diabetes Mellitus was the most common cause of CKD in both groups, 30(37.5%) vs 21(26.3%) in Group-A and Group-B, respectively.

Regarding duration of CKD-5 in both groups' majority of Group-A patients, 43(53.8%), had CKD-5

for 1-3 years, as compared to majority of Group-B patients, 39(48.8%) had CKD-5 for >5 years with dialysis dependency for at least 1 year (p=0.413). Out of the total 80 CKD-5D patients in Group-B, 14(17.5%) were on once weekly maintenance HD, 37(46.3%) were on twice weekly, and 29(36.3%)were undergoing HD thrice weekly. There was a statistically insignificant difference between high diet consumption of both groups, 42(52.5%) vs 48(60.0%) patients of Group-A and Group-B, respectively (p=0.114). Table-I shows parameters that were studied in both groups.

Table-I: Descriptive Parameters of Patients in Both Groups (n=160)

Characteristics		Group-A (CKD-5ND) (n=80)	Group-B (CKD-5D) (n=80)	*p*-value
Age (Years)	(Mean±SD)	53.76±18.26	52.46±17.50	0.667
	≤50 years	32(40.0%)	36(45.0%)	0.589
	>50 years	48(60.0%)	44(55.0%)	
Gender	Male	46(57.5%)	38(47.5%)	0.184
	Female	34(42.5%)	42(52.5%)	
CKD Duration	1-3 years	38(47.5%)	23(28.8%)	0.413
	3-5 years	23(28.8%)	18(22.5%)	
	>5 years	19(23.8%)	39(48.8%)	
Frequency of Hemodialysis	Once weekly	-	14(17.5%)	-
	Twice weekly		37(46.3%)	
	Thrice weekly		29(36.3%)	
Duration of Hemodialysis	2 hours	-	18(22.5%)	-
	3 hours		27(33.8%)	
	4 hours		35(43.8%)	
Diet	Normal Protein	42(52.5%)	32(40.0%)	0.114
	High Protein	38(47.5%)	48(60.0%)	
Uric Acid Levels	Normal (3.0-6.9 mg/dl)	29(36.3%)	47(58.8%)	0.004
	High (≥7.0 mg/dl)	51(63.8%)	33(41.3%)	

**CKD-5ND: Chronic Kidney Disease - Grade 5 non dialysis, CKD-5D: Chronic Kidney Disease - Grade 5 dialysis dependent*

Uric acid levels were checked in all patients, and it was observed that patients in Group-A (CKD-5ND) tended to have higher levels of uric acid compared to those in Group-B (CKD-5D), 51(63.8%) vs 33(41.3%), respectively (p=0.004). The association between hyperuricemia and dialysis-dependent patients was analyzed about the weekly frequency and duration of hemodialysis sessions. It was noted that 9(27.3%) patients undergoing once weekly hemodialysis had higher uric acid levels as compared to patients undergoing twice or thrice weekly hemodialysis, 17(51.5%) and 7(21.2%) respectively (p=0.032) (Table-II).

The duration of every hemodialysis session was an important confounding factor in determining hyperuricemia in hemodialysis. Out of 80(50%) patients of CKD-5D, 18(22.5%) were undergoing 2-hour HD session, 27(33.7%) were 3-hour session, and 35(43.8%) were having maintenance dialysis of 4 hours per session. It was observed that 11(33.3%) patients with 2-hourly sessions had hyperuricemia, 10(30.3%) with 3-hourly sessions, as compared to 12(36.4%) patients receiving 4-hourly sessions, had high uric acid levels (p=0.147) (Table-III).

Measure of association, like Odds ratio (OR) and prevalence ratio (PR), was calculated for the association of hyperuricemia with hemodialysis. Both odds ratio (OR) and prevalence ratio (PR) were <1, indicating there were lower odds and a lower prevalence of hyperuricemia in patients with CKD-5D (OR =0.41, PR =0.65, 95% CI) (Table-IV).

Table-II: Association of Hyperuricemia with Frequency of Hemodialysis in Group-B (n=80)

Frequency of Hemodialysis	Uric Acid levels		Total	*p*-value
	Normal (3.0-6.9 mg/dL)	High (≥7.0 mg/dL)		
Once weekly	5(10.7%)	9(27.3%)	14(17.5%)	0.032
Twice weekly	20(42.5%)	17(51.5%)	37(46.2%)	
Thrice Weekly	22(46.8%)	7(21.2%)	29(36.3%)	
Total	47	33	80	

Table-III: Association of Hyperuricemia with Duration of Hemodialysis Session in Group-B (n=80)

Duration of Hemodialysis	Uric Acid levels		Total	*p*-value
	Normal (3.0-6.9 mg/dL)	High (≥7.0 mg/dL)		
2 hours	7(14.9%)	11(33.3%)	18(22.5%)	0.147
3 hours	17(36.1%)	10(30.3%)	27(33.7%)	
4 hours	23(49.0%)	12(36.4%)	35(43.8%)	
Total	47	33	80	

Table-IV: Measures of Association of Hyperuricemia with Hemodialysis (n=160)

		Hemodialysis		Total
		Yes	No	
Hyperuricemia	Yes	33 (41.3%)	51 (63.8%)	84
	No	47 (58.7%)	29 (36.2%)	76
Total		80	80	160

Odds of Hyperuricemia in Hemodialysis = (33/47) = 0.7
Odds of Hyperuricemia in Non-Hemodialysis = (51/29) = 1.7
Odds Ratio (OR) = Odds in Hemodialysis / Odds in Non-Hemodialysis
OR = 0.7/1.7 = 0.41
Prevalence of Hyperuricemia in Hemodialysis: 33/80 = 0.41
Prevalence of Hyperuricemia in Non-Hemodialysis: 51/80 = 0.63
Prevalence Ratio (PR): Prevalence of Hyperuricemia in Hemodialysis/ Prevalence of Hyperuricemia in Non-Hemodialysis:
PR: 0.41/0.63 = 0.65

DISCUSSION

The study determined, with its findings, that Uric acid has a strong association with renal function and GFR. There is a high prevalence of hyperuricemia in CKD patients, and with declining eGFR, uric acid levels increase. The pooled prevalence of CKD in general population of South Asian countries is 14%. Hyperuricemia is common among CKD patients and has vascular complications concerning the stage of the disease. In this study, hyperuricemia association was

studied in the background of CKD-5 with hemodialysis and without hemodialysis dependency, showing increased prevalence of hyperuricemia in CKD-5ND, which is in accordance with the available literature.

In a study by Doualla *et al.,* it was concluded that the prevalence of hyperuricemia in CKD-5 patients was 81.9% with mean uric acid levels of 78.8±13.8 mg/dl and 66.6 mg/dl, respectively, before hemodialysis and after dialysis, showing a mean clearance of 66%±10%.[12] In our study, it was noted that CKD-5D patients had a lower prevalence of hyperuricemia as compared to CKD-5ND, indicating clearance of uric acid during weekly sessions of dialysis, 30(37.5%) vs 51(63.8%), respectively (p<0.005). In a descriptive cross-sectional study on 200 pre-dialysis CKD patients done by Qayyum *et al.,* it was revealed that 62.5% had hyperuricemia and 37.5% had normal uric acid levels.[13] Among other factors of raised uric acid levels, it was observed that patients consuming a high-protein diet despite maintenance dialysis tend to have raised uric acid levels.

The frequency of weekly hemodialysis being an important confounder of high uric acid levels in CKD patients, it was observed in this study that patients undergoing once weekly hemodialysis had higher levels of uric acid in 9(27.3%) patients as compared to patients undergoing twice or thrice weekly hemodialysis 17(51.5%) and 7(21.2%) respectively. Moon *et al.,* concluded in a study that hyperuricemia was noted in 56(76.7%) patients of CKD-5D undergoing thrice weekly dialysis.[14] Similarly, a population-based study by Qidwai *et al.,* on 2727 Pakistani individuals without CKD reported hyperuricemia in 39% individuals.[15]

A documented fact in literature is that raised uric acid levels are associated with risk of declining eGFR, leading to an increase in CKD stage along with cardiovascular complications and increased mortality. Kuo *et al.,* explained in his study that patients having hyperuricemia had significant annual decline in eGFR 2.5±9.5 ml/min/1.73m^2 per year (2.8±11.6% per year), as compared to patients with normal uric acid levels 1.3± 9.6 ml/min/1.73m^2 per year (1.1±11.1% per year) (p<0.001).[16]

In a retrospective analysis of 6011 patients of CKD-5D done by Rohn *et al.,* it was shown that Cox analysis of patients on chronic dialysis excluded an increased cardiovascular mortality in CKD-5D patients with hyperuricemia.[17] Similarly, in a meta-analysis of 29 studies done by Zhang *et al.,* patients with maximum serum uric acid levels showed significantly higher risk for all-cause mortality (Hazard ratio 1.30, 95% CI) as compared to patients with minimum uric acid levels where no significant association was found between uric acid levels and cardiovascular mortality in CKD patients.[18] Studies like Muhammad *et al.,* showed that in dialysis and renal transplant patients there was inverse relationship of high uric acid levels with all-cause mortality. On the other hand, peritoneal dialysis-related studies implicate a linear relationship between hyperuricemia with mortality.[19]

In this study, measures of association were calculated, which showed that CKD-5D patients had lower odds and a lower prevalence of hyperuricemia in comparison to CKD-5ND patients (OR =0.41). Also, there was a higher incidence of asymptomatic hyperuricemia in CKD patients, but there is insufficient evidence to validate management at the early stage due to very little benefit of pharmacological treatment in asymptomatic hyperuricemia in CKD patients.[20] Although lifestyle modifications, low protein diet, and dialysis in CKD-5 patients can be beneficial in hyperuricemia patients.

LIMITATION OF STUDY

The study presented certain limitations, the most important being the limited sample size. In addition, this study was conducted within a single medical center within a limited duration; hence, it doesn`t represent the exact number of individuals with CKD-5 patients needing Renal replacement therapy and their serum uric acid levels. Peritoneal dialysis is an important method to remove uric acid from body, hence patients on peritoneal dialysis also need to be studied for more accurate results.

CONCLUSION

Uric acid has a strong association with renal function and GFR. There is a high prevalence of hyperuricemia in CKD patients, and with declining eGFR, uric acid levels increase. Hemodialysis clears the uric acid from body, decreasing the prevalence of hyperuricemia in CKD-5 patients undergoing hemodialysis. Patients undergoing thrice weekly maintenance hemodialysis had a lower prevalence of raised uric acid levels about once weekly hemodialysis and CKD patients without hemodialysis.

ACKNOWLEDGEMENT

Authors are thankful to all colleagues in data collection and analysis. We extend our regards to Nephrology Department and Dialysis unit staff and microbiologist and laboratory staff.

Conflict of Interest: None.

Funding Source: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MA & KMR: Data acquisition, data analysis, critical review, approval of the final version to be published.

HAS & MH: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

FNA & ZA: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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