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Original article

Relation of Serum Uric acid level to parameters and stages of chronic kidney disease (CKD)

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Abstract:

Background: The prevalence of chronic kidney disease (CKD) has increased worldwide. This is distressing considering that CKD is an irretrievable condition with high mortality. Objective of this study was to study relation of serum Uric acid (SUA) levels with parameters, stages and progression of Chronic Kidney Disease (CKD).

Material and Methods: This was a cross-sectional and observational study conducted on cohort of patients with Chronic Kidney Disease (CKD) on regular maintenance hemodialysis in tertiary care teaching hopital. This study was conducted over period of one year (January 2018 to December 2018).

Results: A total of 46 patients with diagnosis of CKD were studied over a period of one year. Of them 21 (45.65%) were males and 25 (54.35%) were females. The mean age for male patients were 57.48 (±12.62) and female patients were 55.68 (± 13.77). A total 46 (95.66%) were in stage 5 of renal failure with creatinine clearance less 15 ml/min. and 2 (4.34%) patients were in stage 4.The serum creatinine levels showed positive correlation (+0.44) with uric acid levels and creatinine clearance had negative correlation (-0.38) with uric acid levels.

Conclusion: The serum uric acid levels showed positive correlation with serum creatininelevelshad negative correlation with creatinine clearance and stages of CKD. The uric acid can be considered as a budding therapeutic target to prevent kidney disease onset and progression.

Keywords: Chronic kidney disease, Serum uric acid, Hemodialysis, Creatinine clearance

Introduction:

The prevalence of chronic kidney disease (CKD) has increased and will continue to increase worldwide. This is disquieting considering that CKD is an irretrievable condition with reduced quality of life and high mortality. It is crucial to identify modifiable risk factors to develop strategies to slow the CKD progression like hyperuricemia. The various observational studies have quoted an association of hyperuricemia with kidney disease due to its prevalence in patients with CKD. The experimental studies have shown several probable mechanisms by which hyperuricemia may contribute to the development and progression of CKD. Elevated serum uric level has been suggested as a risk factor for chronic kidney disease

(CKD).Serum uric acid concentrations increase in chronic kidney disease (CKD) and may lead to tubular injury, endothelial dysfunction, oxidative stress, and intrarenal inflammation. In chronic kidney disease (CKD), the direct clinical impact of hyperuricemia is amplified by the comorbidities it shares with CKD like, hypertension, diabetes, and features of the metabolic syndrome. CKD is associated with decreased excretion of uric acid and resultant hyperuricemia. The hyperuricemia is associated with increased risk of progression to ESRD in patients with CKD but uric acid lowering therapy does not ameliorate the risk, suggesting that the relationship is not causal.[1,2]Association between hyperuricemia and chronic kidney disease has been studied inadequately in Indian context. We aimed to find the association between serum uric acid levels and Chronic Kidney Disease Progression.

Material and Methods:

This was a cross-sectional and observational study conducted on cohort of patients with Chronic Kidney Disease (CKD) on regular maintenancehemodialysis. This study was conducted over period of one year (January 2018 to December 2018) in Krishna Institute of Medical Sciences a tertiary care teaching hospital. The study ethical approval was taken from Institutional Ethical committee (IEC). The Informed and written consent were taken from patients before enrolment for study.

The patients fulfilling criteria of chronic kidney disease were enrolled for this study. The patients on drugs which reduce serum uric acid level were excluded from this study. A total of 46 patients with diagnosis of CKD fulfilling inclusion criteria of the study were enrolled over a period of one year.

The patients' clinical characteristics (sex, age, and blood pressure) and chemical parameters (Blood sugar level Lipid profile), microalbuminuria, creatinine, serum sodium (Na^+), serum potassium (K^+) and serum uric acid (SUA) were recorded, and the association between uric acid and CKD was evaluated. The eGFR was calculated for staging the CKD. The eGFR was estimated using the Cockcroft and Gault formula **[**CCr=[((l 40– age) x weight)/(72xSCr)] x 0.85 (if female) [Abbreviations: CCr (creatinine clearance) = mL/minute, Age = years, Weight = kg, SCr (serum creatinine) = mg/dL**]**.[2] The baseline eGFR and CKD stage were based on the first available eGFR. Patients were divided into five groups according to the baseline eGFR using the cut-off values: ≥90, 60±89.9, 30±59.9, 15±29.9 and <15 ml/min per 1.73 m^2.[3,4]

Statistical Analysis: Data Collected was entered in Microsoft Excel. Data was analysed for mean, percentage, standard deviation and chi square test for quantitative data by using Microsoft *excel* spread sheet. Appropriate statistical tests were applied using SPSS software version 21 (trial version) for analysis and 'p' value <0.05 was considered statistically significant.

Results:

A total of 46 patients with diagnosis of CKD were studied over a period of one year. Of them 21 (45.65%) were males and 25 (54.35%) were females, predominated by female gender with male to female ratio of 0.84 (1:1.19). The mean age for male patients were 57.48 (±12.62) and female were female 55.68 (± 13.77) patients.

A total the 44 out of 46 (95.66%) patients were in stage 5 of renal failure with creatinine clearance less 15 ml/min. Of them 20(43.48%) patients, were males and 24(52.18%) were females ('p' = 0.23). Two (4.34%) patients were in stage 4 (2.17%) one was male and one was female. The stage 5 renal failure was predominated in present cohort of patients with CKD ('p'<0.001).

The mean haemoglobin level in male population (8.02 ±1.90 gm %) was higher than females (7.79 ±2.13 gm %). There was no significant difference of mean among genders for quantitative parameters.The mean of Na^+[M:129.43 (±4.95), F:122.76(±22.44)] was

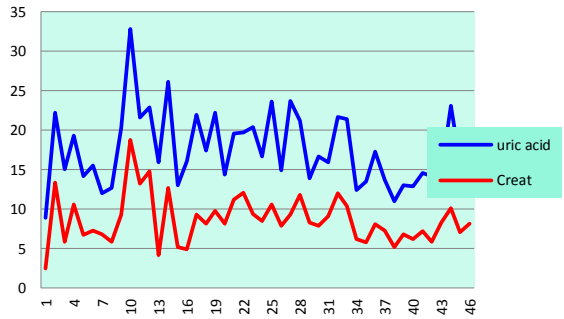
relatively low in female patients compared to male patient. The mean of Uric Acid [M: 8.38 (±2.04), F: 9.23 (±2.73)] was relatively high in female patients compared to male patient. [Table 1]

Table 1: Mean and standard deviation of quantitative data

Variables	Male		Female		Total	
	Mean	(±) SD	Mean	(±) SD	Mean	(±) SD
Age	57.48	12.61	55.68	13.77	54.11	17.92
Haemoglobin	8.02	1.90	7.79	2.13	7.54	0.42
Fe	48.48	17.30	56.20	15.86	54.57	4.80
TIBC	291.52	87.91	295.16	110.14	324.75	62.70
Urea	173.05	49.74	181.20	44.85	185.25	18.87
Creatinine	9.06	3.66	8.33	2.42	8.53	1.24
Na+	129.43	4.95	122.76	22.44	124.32	5.07
K+	5.40	1.06	5.02	0.92	5.16	0.66
Ca++	7.61	0.97	7.88	1.19	7.69	0.67
PO4++	5.86	1.92	6.16	1.74	6.53	0.67
Uric Acid	8.38	2.04	9.23	2.73	8.53	2.96
Creatinine Clearance	9.45	5.70	7.56	2.86	7.96	1.82

The serum uric acid levels showed linear relation with serum creatinine level in cohort of CKD patients.[Figure 1]

Figure1: Correlation between serum creatinine and uric acid levels



Of the various parameters studied, uric acid levels showed strong positive correlation (0.44) withserum creatinine, followed by age (+0.16) and serum potassium (+0.13) after adjusting for confounding factors. The creatinine clearance had negative correlation (-0.38) with uric acid levels.[Table2 and Figure 2]

Table 2: Correlation between serum uric acid levels and quantitative variables

Variable	Correlation with uric acid
Creatinine	0.44
Age	0.16
Iron	0.11
Potassium	0.13
Hb	0.04
Urea	0.05
TIBC	-0.01
Calcium	-0.09
PO4++	-0.11
Sodium	-0.16
Creatinine clearance	-0.38

Figure 2: Correlation of uric acid level with various parameters of patients with CKD

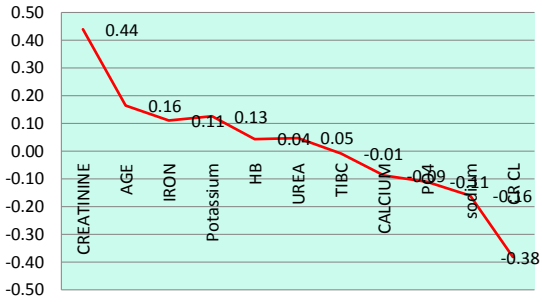


Table 3: Frequency distribution of Levels of serum Uric acid in patients with CKD

Uric acid level (mg)	5.1-8	8.1-11	11.1-14	>14	Total
Total(n)	13	19	12	2	46
%	28.26	41.30	26.09	4.35	100

The majority of patients were had serum uric acid level between 8 to 14 mg (67.39%). [Table 3]

Discussion:

Uric acid has been implicated in the pathophysiology of renal disease. Uric acid is definitively linked to the development of chronic kidney disease and can be a poor prognostic factor for the development of acute renal failure, as well.[4] The prevalence of hyperuricemia and chronic kidney disease (CKD) has been steadily increasing. The role of hyperuricemia and efficacy of uric acid-

lowering agents against CKD progression remain controversial.[5] *Tae Ryom Oh et al* (2019)in their prospective cohort studied the effect of hyperuricemia and uric acid-lowering agents on the progression of CKD (n=2042) patients with CKD in the Korea N cohort Study for Outcomes in patients With Chronic Kidney Disease (KNOW-CKD). They concluded that the hyperuricemia appears to be an independent risk factor for composite renal outcome, but allopurinol and febuxostat did not show reno-protective effect.[5]

In present cohort of patients with CKD uric acid levels showed strong positive correlation (0.44) serum creatinine levels and negative correlation (-0.38) creatinine clearance. Similarly *Giacomo Z et al* (2012)determined whether baseline serum uric acid levels predict the subsequent development of CKD in patients with type 2 diabetes (n=1,449) with normal kidney function and without overt proteinuria for 5 years for the occurrence of incident CKD.They found that the 13.4% patients developed incident CKD (P< 0.001). In univariate logistic regression analysis, the presence of hyperuricemia roughly doubled the risk of developing CKD.[6] In present cohort of patients with CKD uric acid levels showed strong positive correlation (0.44) serum creatinine levels. *Sheikhbahaei S et al* (2014)studied the relationship of serum uric acid (SUA) with an increased prevalence of metabolic risk factors, albuminuria, and chronic kidney disease (CKD) and found that there was a significant, graded increase in odds of CKD by increasing SUA levels and the number of metabolic syndrome risk factors ('p'<0.001).[7]Similar to present study, *Yan D et al* (2015)in their cross-sectional study (n= 3,212) observed that, the prevalence of diabetic kidney disease was higher in hyperuricaemic patients than in patients with normouricaemia (68.3% vs 41.5%). Uric acid was positively correlated with albuminuria and creatinine levels (p < 0.0001) but negatively correlated with eGFR (p < 0.0001). Hyperuricaemia is a risk factor for CKD. Serum uric acid levels within the high-normal range are independently associated with CKD.[8]

Petreski T et al(2019)studied 120 CKD patients retrospectively (83 CKD patients; 33 female an 50 male) and concluded an association between hyperuricemia and cardiovascular mortality in CKD patients who transition to hemodialysis.[9] *Luo Q et al* (2012)in their systematic review (meta-analysis) included 11 studies (n=27,081) with CKD patients quoted that, the higher SUA levels are associated with significantly increased risk of cardiovascular mortality in patients with CKD.[10] *Mok Y et al* (2012)in their prospective cohort study(n=14 939) in Koreans. The CKD (an estimated glomerular filtration rate (GFR) of <60 mL/min/1.73m) observed that the higher SUA levels increased the risk of CKD.[11

]*Satirapoj B et al*in their cross-sectional studyin southeast Asian population (n=5546)concluded that the, high serum uric acid level was independently associated with increased prevalence of CKD. Detection and treatment of hyperuricaemia should be attended as a strategy to prevent CKD.[12]Similarly in present study uric acid levels showed positive correlation (0.44) serum creatinine levels and negative correlation (-0.38) creatinine clearance. *Srivastava A et al* (2018) in their prospective observational cohort study (n=3,885) individuals with CKD stages 2 to 4 were enrolled in the Chronic Renal Insufficiency Cohort (CRIC).They observed that the SUA is an independent risk factor for kidney failure in earlier stages of CKD.[13]

Theodoros E et al (2017) Today there is plausible evidence both on experimental and epidemiological basis, that hyperuricemia represents a risk factor for the development and progression of chronic kidney disease (CKD). Review of randomised controlled trials, suggests that there may be an improvement of renal function with

allopurinol treatment in CKD stage 3–5.[14] *Ching W T et al* (Taiwan 2017) studied 739 patients and concluded that, a higher uric acid level is associated with a significant rapid decline in eGFR and a higher risk of kidney failure. The hyperuricemia is a potential modifiable factor of CKD progression. These findings are comparable with present study.[15]

Similarly *Sedaghat S et al* (2013)included 2601 subjects aged 55 years and over from the Rotterdam Study. They observed that the associations of serum uric acid with eGFR decline and incident CKD were stronger in hypertensive subjects. They suggest that hyperuricemia is independently associated with a decline in renal function.

Stronger association in hypertensive individuals may indicate that hypertension mediates the association between serum uric acid and CKD.[16] *Xiaole Su et al* (2017) in their systematic review and meta-analysis studied the effects of uric acid-lowering therapy in patients with chronic kidney disease (CKD) and quoted that the Uric acid-lowering therapy seemed to improve kidney outcomes and reduce the risk of cardiovascular events in adults with CKD.[17] [Table 4]

Table 4:Comparison of various studies
[5,15,6,8,13,16,17,11,7,14,10,9]

	Study author	Population	Findings and Interpretation
1.	Tae Ryom Oh et al	2042 (KNOW-CKD)	The hyperuricemia appears to be an independent risk factor for composite renal outcome.
2.	Ching-WT et al	739	Higher uric acid level is associated with a significant rapid decline in eGFR and a higher risk of kidney failure.
3.	Giacomo Z et al	1449	The presence of hyperuricemia roughly doubled the risk of developing CKD.
4.	Yan D et al	3212	The prevalence of CKD was higher in hyperuricemic patients is a independent risk factor for CKD.
5.	Srivastava A et al	3885	The SUA is an independent risk factor for kidney failure in earlier stages of CKD.
6.	Sedaghat S et al	2601	An association of serum uric acid with eGFR decline and incident CKD were stronger in hypertensive subjects.
7.	Xiaole Su et al	Systematic review	Uric acid-lowering therapy seemed to improve CKD outcomes.
8.	Mok Y et al	14 939	The higher SUA levels increased the risk of CKD.
9.	Sheikhbahaei S et al	1463	A synergistic effect and graded increase in odds of CKD by increasing serum uric acid levels and number of metabolic syndrome risk factors.
10.	Theodoros E et al	-	There may be an improvement of renal function with allopurinol treatment in CKD stage 3–5.
11.	Luo Q et al	11 studies (meta-analysis)	SUA levels are associated with significantly increased risk of cardiovascular mortality in patients with CKD
12.	Petreski T et al	120	An association between hyperuricemia and cardiovascular mortality in CKD patients.

Hyperuricemia is associated with the development and progression of chronic kidney disease (CKD) as well as cardiovascular diseases. Most Korean physicians treat asymptomatic hyperuricemia (AHU) in CKD patients to prevent CKD progression and cerebro-cardiovascular complications.[18] Uric acid is a product of purine metabolism and has been linked to gout and kidney calculi. Chronic kidney disease (CKD) and hypertension (HTN) are two major public health problems.
Emerging evidence suggests a pathogenic role of hyperuricemia in the development of HTN and CKD, in addition to progression of CKD, by inducing renal inflammation, endothelial dysfunction, and activation of the renin-angiotensin system. A few clinical trials have assessed the use of uric acid-lowering therapies such as allopurinol and febuxostat in the management of HTN and delaying progression of CKD.[19] Epidemiologic and clinical studies have suggested that urate-lowering therapy may slow the progression of

chronic kidney disease (CKD), nevertheless the definitive evidence is lacking.[20]

Elevated serum uric acid levels are significantly associated with risk of mortality in patients with CKD.[21] Hyperuricemia is a contributor to the development and progression of CKD. Lifestyle modification such as exercise, weight reduction, low consumption of purine-rich meat, or avoiding high fructose intake are recommended for all hyperuricemic patients. Lowering urate may be an option as a reno-protective agent. There is inadequate evidence to recommend the use of UA-lowering therapy to slow down the progression of CKD.

Conclusion:

Two third of cohort with CKD in present study had serum uric acid level between 8 to 14 mg/dl.Majority of the patients were in stage 5 of renal failure. The serum uric acid levels showed positive correlation with serum creatinine levels, age and serum potassium. The Creatinine clearance had negative correlation with uric acid levels. The uric acid can be considered as a budding therapeutic target to prevent kidney disease onset and progression. The potential nephro-protective effect of decreasing uric acid levels in patients with CKD will be promising.

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