Research article

The Bidirectional Relationship between Serum Uric Acid Levels and Kidney Function Markers: A Predictive Model for Chronic Kidney Disease Progression

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Abstract | Numerous have examined the link among chronic kidney disease (CKD) and hyperuricemia, although the precise relationship is unknown. The present study aimed to discover whether they were directionally connected or not. This study followed adults aged 18 and above with CKD stages (1-4) over a period of 12 months. It has been conducted in Al-Kindi Teaching Hospital- Baghdad / Iraq, during the period (2022-2023). Data, on demographics, clinical information and lab results including serum acid levels and estimated glomerular filtration rate (eGFR) were gathered at the beginning. The participants were monitored for changes in these factors over time. The study consisted of 342 individuals. A reciprocal association was identified between eGFR and levels of uric acid. ($p<0.001$). The receiver operating characteristic curve (ROC) showed that serum uric acid predicted renal function at 7.5 mg/dl. In a logistic regression model, elevated uric acid levels independently increased renal dysfunction risks. This study provides evidence for a bidirectional relationship between serum uric acid and kidney function markers. Uric acid demonstrated good predictive accuracy for identifying impaired renal function, highlighting its potential utility as a risk factor or prognostic marker for CKD progression. The development of a predictive model incorporating uric acid could inform clinical management strategies to mitigate CKD progression.

Keyword: CKD, Chronic kidney disease, Uric acid levels, Kidney function

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INTRODUCTION

Chronic kidney disease is distinguished by a function of one or more indicators of kidney injury persisting for a minimum of three months or a GFR below 60 ml/min/1.73 m^2. Anomalies in kidney structure or histology, albuminuria, and aberrant urine sedimentation are examples of such predictors (1). Individuals diagnosed with CKD frequently experience the presence of cardiovascular disease (CVD) and eventually advance to end-stage kidney disease (ESKD). Consequently, CKD poses a significant mortality risk and imposes a substantial cost on individuals affected by it. This has emerged as a pressing public health issue that needs to be addressed in China and globally (2, 3). In recent decades, there has been a steady rise in the worldwide occurrence of CKD and the associated mortality rate. The worldwide incidence of CKD in the year 2017 was 9.10%. Between 1990 and 2017, the international mortality percentage for CKD in all age groups grew by 41.50% (4, 5). While the exact cause of CKD is not yet fully understood, it is important to identify and intervene in the risk factors of CKD in order to prevent or postpone its onset and progression. This can effectively lower the risk of mortality and the overall burden of the disease (6).

Both metabolic syndrome and cardiovascular disease were found to be significantly predicted by hyperuricemia (7). Serum uric acid increased with the risk of CKD, despite the fact that It was an independent CKD risk factor (8, 9). Consequently, multiple investigations conducted on different groups of people have demonstrated a notable rise in the likelihood of hyperuricemia in individuals with CKD or a decreased eGFR (10, 11).

The results in this cohort research include hyperuricemia and CKD, suggesting a reciprocal link, to assess the link between CKD, eGFR, and hyperuricemia. After baseline and first-round follow-up measurements, It has been validated the causal relationship and bidirectional interaction between eGFR and uric acid.

PATIENTS AND METHODS

Study Design And Setting

This cohort research estimated the independent and bidirectional interaction of serum uric acid with kidney function measures as variables in CKD development over 12 months. This study was conducted in Al-Kindi Teaching Hospital- Baghdad / Iraq, during the period (2022-2023). The Declaration of Helsinki ethical norms and hospital Institutional Review Board approval were followed for the research.

Participants

Enrolled eligible 324 participants were adults aged 18 years and above, diagnosed with stages 1–4 CKD. An exception was made for patients who had ever been diagnosed with gout or put on uric acid-lowering therapy, patients on dialysis, having kidney transplantation, and patients who had ever diagnosed with any malignancy. Enrolment was voluntary, with consent was obtained from all participants.

Data Collection

Baseline characteristics, containing demographics (age, sex, BMI), medical history (comorbid conditions, medication use), and lifestyle factors (diet, physical activity), were collected by interviewing the patients and reviewing medical records and laboratory measurements.

Serum uric acid and several indicators of kidney function (eGFR, creatinine) were measured at baseline and every 6 months. The quantification of uric acid was performed through an enzymatic colorimetric technique, while the estimation of eGFR was derived from the CKD-EPI equation.

Study Outcomes And Related Definitions

An abnormal eGFR of 60 or proteinuria with a urine dipstick value of 1+ or greater were utilized to define CKD in this study. By integrating the initial and first follow-up estimates, the type of eGFR alterations was ascertained. According to globally recognized epidemiological diagnostic standards, hyperuricemia was defined as serum uric acid (mg/dl) levels exceeding 7 in men and 5.5 in females. Levels within these limits were deemed normal. The dynamic variations in uric acid were categorized using baseline and follow-up data.

Predictive Model Development

The study's main goal was to develop and test a prediction model for CKD progression, defined as a 30% or larger drop in baseline eGFR, a higher CKD stage, or dialysis beginning.

Demographics, renal function indicators, and baseline serum uric acid were predictors. This bidirectional approach examined how kidney function declines affect serum uric acid levels throughout time. In statistical analysis, the study population's baseline characteristics were characterized using descriptive statistics. Binary logistic regression models linked serum uric acid to kidney function indicators. A two-tail p-value below 0.05 in SPSS version 27.0 analyses signified statistical significance.

RESULTS

Hyperuricemia group had a substantially older mean age (62.83 ±5.8 years) compared to the non-hyperuricemia group (58.83 ±6.4 years) (p=0.045). Hyperuricemia showed a significantly greater proportion of male participants (73.7%) than non-hyperuricemia (67.4%) (p=0.032). Both diabetes (68.8%) and hypertension (73.8%) were more common in the hyperuricemia group. Laboratory data, the Hyperuricemia group exhibited significantly worse lipid profile parameters. They had higher lipid profile parameters p<0.001). The Hyperuricemia group also had lower eGFR, mL/min/1.73m^2 (64.42 ±11.5 vs. 83.39 ±11.9, p<0.001). Patients with levels of uric acid showed lower estimated glomerular filtration rates (eGFR). Additionally, the occurrence of CKD was notably higher among these individuals during both the initial assessment and subsequent follow-up periods of uric acid measurement. The statistical analysis of these findings was significant (p < 0.001) across all parameters analyzed (Table 1).

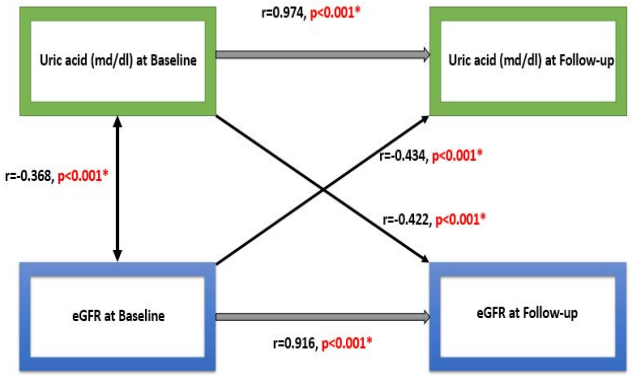

Figure 1: A bidirectional relationship between uric acid and eGFR.

Figure 2 displays the ROC curve for the predictors of impaired renal function, specifically uric acid. In the begin

Table 1: Patient's characteristics were analyzed based on hyperuricemia presence.

Variables		Non-hyperuricemia N=187	Hyperuricemia N=137	p value
Demographic				
Age (years)		58.83 ±6.4	62.83 ±5.8	0.045*
BMI (kg·m-2)		23.37 ±1.7	25.43 ±1.9	0.823
Gender	male	126 (67.4%)	101 (73.7%)	0.032*
	female	61 (32.6%)	36 (26.3%)	
Risk Factors				
Smoker		62 (33.2%)	67 (48.9%)	0.002*
Diabetes		99 (52.7%)	94 (68.8%)	0.001*
Hypertension		119 (63.8%)	101 (73.8%)	0.004*
Clinical data				
Systolic blood pressure (mmHg)		122.54 ±10.5	132.43 ±11.3	<0.001*
Diastolic blood pressure (mmHg)		82.98 ± 8.2	83.87 ±7.9	0.076
Laboratory data				
Total Cholesterol (mg/dl)		187.43 ± 11.4	231.43 ±12.9	<0.001*
Triglycerides(mg/dl)		138.73 ±7.8	159.63 ±9.4	<0.001*
Low-Density Lipoprotein (LDL) (mg/dl)		91.87 ±4.5	110.87 ±4.9	<0.001*
High-Density Lipoprotein (HDL) (mg/dl)		45.98 ±3.8	34.38 ±5.9	<0.001*
Uric acid (mg/dl)		5.36 ±2.5	7.94 ±2.8	<0.001*
eGFR, mL/min/1.73m^2		83.39 ±11.9	64.42 ±11.5	<0.001*
eGFR<60 mL/min/1.73m^2		8 (4.3%)	28 (20.4%)	<0.001*
CKD at Baseline		8 (4.3%)	43 (31.4%)	<0.001*
CKD at follow up		9 (4.8%)	51 (37.2%)	<0.001*

Data represent the mean ±stander deviation or Number (%).

*: Statistically significant at p ≤ 0.05.

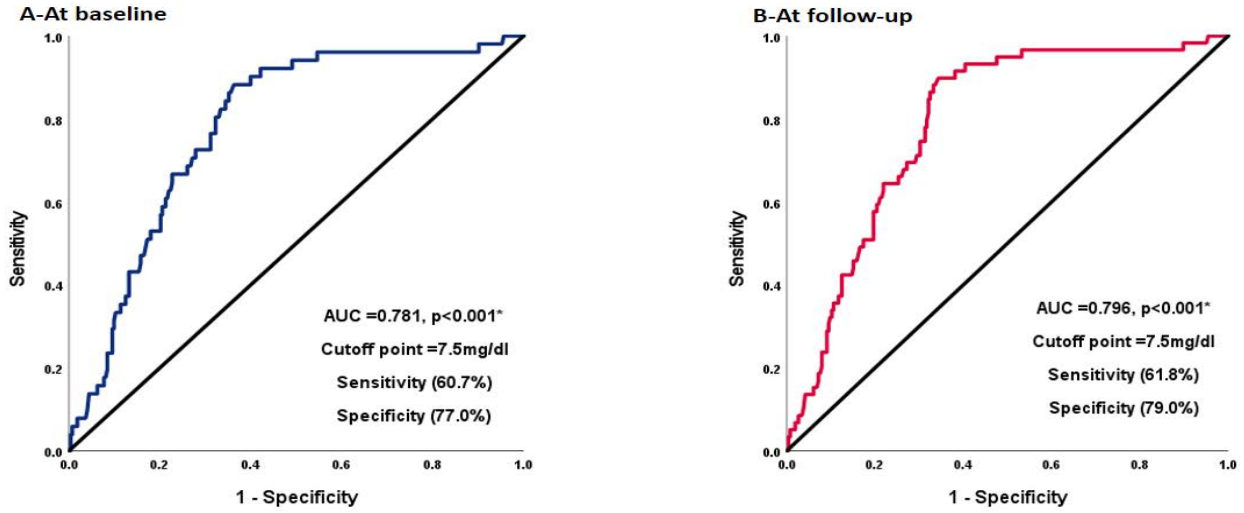

Figure 2: Roc curve analyses of serum uric acid for the prediction of kidney impairment at baseline compared to at follow up

Table 2: Analysis of Multivariable and Univariable Logistic Regression for impaired Kidney Function

	Model -1			Model- 2			Model -3		
	OR	95%-CI	P value	OR	95%-CI	P value	OR	95%-CI	P value
Uric acid	1.747	(1.413-2.159)	<0.001*	1.762	(1.424-2.181)	<0.001*	1.021	(1.10-1.198)	0.002*

Model 1 is unadjusted; Model 2 is basic, adjusted for sex and age; Model 3 is completely adjusted.

ning the test displayed an accuracy of 0.781, at the baseline (A). The optimal cut off threshold, 7.5 mg/dl, had 82.6% sensitivity and 77.9% specificity. With this threshold, the test can detect 82.6% and 77.9% of cases. Interesting, during follow-up (B), The Area under Curve (AUC) increased to 0.796, showing diagnostic performance. The best cut off is 7.5 mg/dl with 81.8% sensitivity and 79.0% specificity.

As shown in Table 2, a logistic regression model examined how uric acid affects renal dysfunction in patients. A substantial positive connection was found between uric acid and renal impairment in the crude model. After controlling for sex and age, the positive connection remained significant in Model 2. Model 3, with additional adjustments for all covariates, had a similar association to the baseline model.

DISCUSSION

Chronic kidney disease and hyperuricemia were strongly linked in this research. The relationship between eGFR, serum uric acid, and CKD was intriguing in a prospective cohort analysis.

Purine metabolism in the human body produces uric acid, which is mainly removed by the kidneys. Uric acid excretion may be impeded when renal function is inadequate or diminishes. This may cause the level of uric acid to rise and hyperuricemia to manifest. According to the current study, people with CKD were far more likely than people without CKD to experience hyperuricemia (13).

Furthermore, various cross-sectional studies (11, 14, 15) have revealed a clear link between renal insufficiency and the risk of hyperuricemia. This risk becomes more pronounced as eGFR decreases. Nevertheless, the studies solely focused on examining the link between low eGFR (<60) and the risk of hyperuricemia, without delving into the potential connection between high eGFR and hyperuricemia.

Previous research has indicated that a higher eGFR can serve as an indicator for cardiovascular disease (16) and hypertension (17). However, limited information is presently accessible with respect to the link between a higher eGFR and the risk of hyperuricemia. We discovered that there were significant associations between hyperuricemia and eGFR. The group with Hyperuricemia exhibited a lower eGFR of mL/min/1.73m^2 compared to the other group (64.42 ±11.5 vs. 83.39 ±11.9, p<0.001). Patients who had higher levels of uric acid exhibited decreased estimated glomerular filtration rates (eGFR).

A study by Har et al., (18) indicated that GFR hyperfiltration can result in elevated intra-glomerular pressure, as well as higher levels of tubular markers lsljin individuals with hyperfiltration compared to those without (19). In addition, it can result in proteinuria and decreased renal function (20). Thus, high eGFR and hyperuricemia in this research may be due to renal damage from GFR hyperfiltration hindering uric acid excretion. More research with bigger sample numbers are needed to validate these results and understand the processes behind these correlations.

Research suggests that uric acid may damage kidneys and cause CKD. Urate crystals may obstruct renal tubules, affect vascular smooth muscle cell proliferation, and lower endothelial NO levels. Renin-angiotensin-aldosterone system activation is also detected in uric acid. Our results may be biologically justified by these methods (21, 22).

This findings is in accordance with Ma et al., (23) reported that In individuals with hyperuricemia, the adjusted hazard ratio (adjusted HR) for CKD was 1.28 (1.124–1.472). For those with 7.5 mg/dl uric acid compared to 2 mg/dl, the adjusted HR of CKD was 1.24 (1.011–1.513). The results align with prior research conducted by various studies (24-26). To explore the relationship between indicator dynamics and illness, frequent assessments are needed. This method reduces reverse causality and improves accuracy and reliability. In a Taiwanese research, (27), researchers measured uric acid levels multiple times. Uric acid levels beyond the clinical cut-off values at baseline and follow-up were associated with a considerably increased risk of CKD. Sustainable eGFR decline increased hyperurecemia risk. CKD was more common in these individuals at baseline and follow-up uric acid ()p < 0.001).

In this study, the results of the bidirectional correlation (uric acid-eGFR) were described. Baseline eGFR and uric acid both had an impact on follow-up eGFR. A retrospective study by Mat et al., (23) discovered a reciprocal connection between uric acid and eGFR. This was achieved by utilizing a cross-lagged model, which effectively accounted for the autoregressive properties of the variables. Through the process of comparing the variances of the cross-lagged coefficients of paths, the study was able to determine the direction of the primary causal effect, assuming that the time-series relationship was evident.

From the results of this research, ROC curve for uric acid predictors of renal dysfunction. Initial test accuracy was 0.781. The optimal cut off point was 7.5 mg/dl, with 82.6% sensitivity and 77.9% specificity. With this threshold, the test can identify 82.6% and 77.9% of cases. Interesting, during follow-up, the AUC improved to 0.796, showing diagnostic performance. The optimum cut off is 7.8 mg/dl with 81.8% sensitivity and 79.0% specificity. The results of this research closely align with Ephraim et al.,(28) found

that Uric acid, Uric acid to creatinine ratio (UA/CR), and Ultra-high resolution (UHR) ROC curves indicate decreased renal function (eGFR <60). In disease prediction, higher AUC values indicate better performance. Uric acid had the highest AUC (0.762) of the three measures. UHR had a larger AUC (0.713) than UA/CR (0.148, $p < 0.001$). The graph shows that uric acid predicts CKD best, whereas UHR surpasses UA/CR.

The binary logistic regression model for this study examined how uric acid affects renal impairment. The crude model revealed a substantial positive connection between uric acid and renal impairment likelihood. After controlling for sex and age, the positive connection remained significant in Model 2. The association between Model 3, which adjusted all covariates, and the baseline model remained largely unchanged (OR, 1.021; P=0.002). Compared to Han et al., (29) Utilizing a logistic regression model, the effect of UA, UA/CR, and UHR on renal impairment in T2DM patients was examined. Significant positive correlations were found between UA and UHR and the risk of renal impairment in the naive model. Model 2 demonstrated a statistically significant positive correlation when accounting for variables such as sex, age and blood pressure. The relationship remained relatively unchanged when other laboratory variables were accounted for in Model 3, as compared to the naive model. In the unadjusted model, UA/CR was inversely associated with the risk of renal impairment. This association remained significant even after controlling for age, sex, BMI, SBP, and DBP. A negative association persisted even after accounting for all variables.

CONCLUSIONS

The current study explored the two-way relationship between CKD and hyperuricemia. Also, provided evidence for the connection between eGFR and serum uric acid. based on the findings presented, CKD and eGFR have the potential to serve as indicators for predicting the probability of hyperuricemia. It is important to consider the management of hyperuricemia and uric acid when preventing and controlling CKD. Properly treating hyperuricemia can help prevent chronic kidney disease and slow down the decline of kidney function.

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

NOVELTY STATEMENT

This discovery holds significant value in terms of guiding early prevention measures for hyperuricemia and identifying individuals at high risk.

AUTHORS CONTRIBUTION

All authors contributed equally.

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