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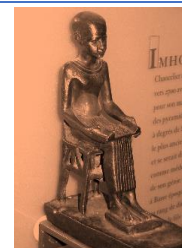
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## Original Article

# Correlation between Serum Uric Acid and Left Ventricular Hypertrophy/Left Ventricular Diastolic Dysfunction in Patients with Chronic Kidney Disease

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## ABSTRACT

### Article information

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**Background:** Serum uric acid [SUA] levels are frequently elevated in patients with chronic kidney disease [CKD]. Higher levels of SUA have been associated with cardiovascular disease. However, the direct relationship between SUA and left ventricular [LV] hypertrophy and diastolic dysfunction in CKD patients remains unclear.

**Aim of the work:** To investigate the correlation between serum uric acid levels and LV hypertrophy as well as LV diastolic dysfunction in CKD patients with preserved LV systolic function.

**Patients and Methods:** We studied 90 CKD patients with estimated glomerular filtration rate less than 60 ml/min/1.73 m<sup>2</sup> and normal LV ejection fraction. Patients were divided into 3 groups according to their SUA levels: less than 10 mg/dl, 10-15 mg/dl, and more than 15 mg/dl. All patients underwent comprehensive transthoracic echocardiography including tissue Doppler imaging for the assessment of LV hypertrophy, geometry, and diastolic functions.

**Results:** Left ventricular end-diastolic diameter, left ventricular mass index, and left atrial volume index were significantly higher in patients with SUA >15 mg/dl. Mitral peak early diastolic velocity, mitral annular early diastolic velocity, and E/e' ratio were significantly altered in patients with SUA >15 mg/dl, indicating impaired LV relaxation and increased filling pressures.

**Conclusion:** Higher serum uric acid levels are significantly associated with increased LV hypertrophy and diastolic dysfunction in CKD patients with preserved ejection fraction. Serum uric acid may play a role in the development of cardiovascular complications in this population.

**Keywords:** Chronic Kidney Disease; Left Ventricular Hypertrophy; Uric Acid.



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## INTRODUCTION

Cardiovascular disease [CVD] is the leading cause of mortality among individuals with chronic kidney disease [CKD] [1]. Those with CKD face a significant burden from conventional risk factors for CVD, in addition to factors related to their kidney condition, including inflammation, elevated calcium and phosphorus levels, uremic toxins, anemia, and fluid overload [2].

The cardiovascular system is intricately linked to kidney function, with renal dysfunction potentially leading to structural and functional issues in the heart that can further impair kidney performance [3]. Among the various cardiac issues faced by patients with chronic kidney disease [CKD], left ventricular hypertrophy [LVH] and left ventricular diastolic dysfunction [LVDD] are prevalent and significantly associated with higher rates of cardiovascular mortality in these individuals [2, 4].

Therefore, identifying the predictors of left ventricular hypertrophy [LVH] and left ventricular diastolic dysfunction [LVDD] is crucial for assessing cardiovascular risk in patients with chronic kidney disease [CKD]. Uric acid, which is the final product of purine metabolism in humans, often accumulates in patients with CKD because of reduced clearance [5].

In addition to its involvement in gout, previous epidemiological studies have indicated that elevated serum uric acid [SUA] levels are a risk factor for several cardiovascular conditions, such as hypertension, metabolic syndrome, coronary artery disease, cerebrovascular disease, vascular dementia, and kidney disease [6].

While previous studies have found associations between elevated SUA and increased prevalence of LVH or LVDD in various populations, few have specifically examined this relationship in pre-dialysis CKD patients with normal ejection fraction. The objective of this study was to examine the relationship between SUA levels and left ventricular hypertrophy as well as left ventricular diastolic dysfunction in individuals with CKD.

## PATIENTS AND METHODS

### Study Population

This cross-sectional study included 90 patients diagnosed with stages 3-4 chronic kidney disease [CKD] with preserved left ventricular systolic function. Patients were recruited from the nephrology outpatient clinic, Al-Azhar University Hospitals between April 2021 and October 2022.

**Inclusion Criteria:** Patient's age > 18 year's old, all study subjects had stages 3-4 CKD [eGFR < 60

mL/min/1.73 m<sup>2</sup>] which determined by MDRD study equation.

**Exclusion Criteria:** Patients on dialysis, Patients with acute kidney injury and Patients diagnosed cardiovascular disease, evidence of systolic heart failure [ejection fraction < 50%] and atrial fibrillation. ongoing or recent treatment with medications affecting uric acid levels [e.g., allopurinol] or gout.

**Ethical Considerations:** Written or informed consent was taken from all patients after explaining the aim of study. Approval of the study protocol was obtained by Ethical Scientific Committee of Faculty of Medicine, Al-Azhar University.

### Data collection

**Serum Uric Acid Measurement:** Serum uric acid levels were measured using standard laboratory methods. Patients were categorized into three groups based on their serum uric acid levels: Group 1: <10 mg/dL, Group 2: 10–15 mg/dL, and Group 3: >15 mg/dL.

### Echocardiographic Assessment

Two-dimensional echocardiography and tissue Doppler imaging were performed by experienced cardiologists using an [Philips iE 33 Xmatrex machine [Philips, Philips IE 33 Ultrasound, Bothell, Washington, USA] ultrasound system. All echocardiographic assessments were conducted in accordance with the American Society of Echocardiography guidelines [7] and was analyzed by an experienced cardiologist who was blinded to clinical details. The following parameters were measured for the assessment of left ventricular hypertrophy [LVH] and diastolic dysfunction:

- Left Ventricular Hypertrophy [LVH]
  - Left ventricular mass [LVM] was calculated using the ellipsoid formula:  $LVM [g] = 0.8 \times [1.04 \times [LVID + PWT + IVST]^3 - [LVID]^3] + 0.6$ .
  - LVH was defined as LVM indexed to body surface area [LVM/BSA] > 115 g/m<sup>2</sup> for men and > 95 g/m<sup>2</sup> for women [7].
- Left Ventricular Diastolic Dysfunction
  - Diastolic function was assessed using transmitral Doppler evaluation to measure the peak velocities of early [E] and late [A] diastolic filling. The E/A ratio was calculated.
  - Tissue Doppler imaging was used to measure early diastolic velocity [E'] at the mitral annulus. The E'/E' ratio was calculated to assess left atrial pressure [7].

## Statistical analysis

Data were analyzed using SPSS version 25. Descriptive statistics were expressed as means  $\pm$  standard deviations for continuous variables and frequencies [%] for categorical variables. Comparisons between groups for continuous variables were conducted using one-way ANOVA, with post hoc analysis using Tukey's test where appropriate. Categorical variables were analyzed using the Chi-square test. A p-value of  $<0.05$  was considered statistically significant.

## RESULTS

In the current study, the 90 patients with pre-dialysis chronic kidney disease were classified into three distinct groups based on their serum uric acid levels. The first group comprised 47 patients with serum uric acid levels below 10 mg/dL, the second group included 34 patients with levels ranging from 10 to 15 mg/dL, and the third group consisted of 9 patients with serum uric acid levels exceeding 15 mg/dL.

The age and body surface area were significantly higher in the group with serum uric acid levels under 10 mg/dL [ $58.32\pm 9.58$  years and  $1.89\pm 0.16$  m<sup>2</sup>] compared to

the 10–15 mg/dL group [ $51.65\pm 8.34$  years and  $1.86\pm 0.18$  m<sup>2</sup>] and the group with levels above 15 mg/dL [ $52.67\pm 8.00$  years and  $1.85\pm 0.18$  m<sup>2</sup>], with a significance level of  $P=0.004$ . Additionally, the majority of participants in the study were male, accounting for 60.00% of the cases, which also showed a significant difference [ $P=0.001$ ] [Table 1].

C-reactive protein levels were significantly higher in the group with serum uric acid levels  $> 15$  mg/dL compared to both the group with levels  $< 10$  mg/dL and the 10–15 mg/dL group [ $p$ -value  $< 0.05$ ]. However, there were no significant differences observed among the groups in relation to other laboratory tests [Table 2].

The left ventricular end-diastolic diameter and left atrial volume index were significantly higher in the group with uric acid levels greater than 15 mg/dL compared to the groups with levels below 10 mg/dL and between 10–15 mg/dL [ $P<0.05$ ]. In contrast, the mitral valve flow E wave velocity, A wave velocity, and peak velocity of early diastolic mitral annular motion, as measured by pulsed wave Doppler, were significantly elevated in the group with uric acid levels under 10 mg/dL when compared to the 10–15 mg/dL and greater than 15 mg/dL groups [ $P < 0.05$ ] [Table 3].

**Table [1]:** Socio demographic data, clinical examination and medication use of cases among serum uric acid values studied groups [n=90]

Variables		Serum uric acid values			Test	P value
		<10 mg/dL [n=47]	10–15 mg/dL [n=34]	>15 mg/dL [n=9]		
Age [years]	Mean $\pm$ SD	58.32 $\pm$ 9.58	51.65 $\pm$ 8.34	52.67 $\pm$ 8.00	5.839	<b>0.004*</b>
	Range	38.00-75.00	39.00-65.00	42.00-58.00		
Post hoc		P1=0.001*, P2=0.088, P3=0.763				
BSA [m <sup>2</sup> ]	Mean $\pm$ SD	1.89 $\pm$ 0.16	1.86 $\pm$ 0.18	1.63 $\pm$ 0.14	9.282	<b>&lt;0.001*</b>
	Range	1.56-2.17	1.51-2.02	1.46-1.78		
Post hoc		P1=0.345, P2 <b>&lt;0.001*</b> , P3 = <b>0.001*</b>				
Sex, n [%]	Male	20 [57.5%]	28 [82.4%]	6 [66.7%]	13.206	<b>0.001*</b>
	Female	27 [42.5%]	6 [17.6%]	3 [33.3%]		
HTN, n [%]	No	19 [40.4%]	11 [32.3%]	0 [0%]	37.312	<b>&lt;0.001*</b>
	Yes	28 [59.6%]	23 [67.7%]	9 [100%]		
DM, n [%]	No	30 [63.8%]	3 [8.8%]	6 [66.7%]	26.526	<b>&lt;0.001*</b>
	Yes	17 [36.2%]	31 [91.2%]	3 [33.3%]		
SBP [mmHg]	Mean $\pm$ SD	136.81 $\pm$ 20.84	147.50 $\pm$ 21.26	153.33 $\pm$ 6.61	4.233	<b>0.018*</b>
	Range	110.0-180.0	115.-190.	145.0-160.		
Post hoc		P1= 0.021*, P2= 0.027*, P3= 0.441				
DBP [mmHg]	Mean $\pm$ SD	80.32 $\pm$ 13.45	83.97 $\pm$ 13.1	85 $\pm$ 7.5	1.033	0.360
	Range	60 -110	65.-100	75-90		
Post hoc		P1= 0.212, P2= 0.321, P3= 0.832				

BSA: Body surface area. CKD: Chronic kidney disease. HTN: Hypertension. DM: Diabetes mellitus. CVD: Cardiovascular disease. IHD: ischemic heart disease. CCB: Calcium channel blockers. F: ANOVA F test. X<sup>2</sup>: Chi-square test. \*Significant. CI: Confidence interval for Mean; SBP: Systolic blood pressure. DBP: Diastolic blood pressure.

**Table [2]:** Laboratory Investigations and estimated glomerular filtration rate of cases in relation to serum uric acid values

Variables		Serum uric acid values			F	P value	95% CI	
		<10 mg/dL [n=47]	10–15 mg/dL [n=34]	>15 mg/dL [n=9]			Lower	Upper
<b>Hemoglobin</b>	Mean ±SD	11.03±1.82	11.32±1.35	11.00±1.26	0.371	0.691	10.80	11.47
	Range	8.50-14.60	8.50-14.30	9.60-12.50				
<b>Post hoc</b>		P1=0.415, P2=0.962, P3=0.592						
<b>Calcium</b>	Mean ±SD	8.94±0.53	9.09±0.42	8.73±0.44	2.292	0.107	8.87	9.08
	Range	8.10-9.80	8.50-10.00	8.30-9.30				
<b>Post hoc</b>		P1= 0.156, P2= 0.247, P3= 0.053						
<b>iPTH</b>	Mean ±SD	118.33±73.13	131.23±77.12	126.00±49.39	0.313	0.732	108.83	139.11
	Range	27.90-287.00	50.20-287.00	65.00-178.00				
<b>Post hoc</b>		P1= 0.434, P2= 0.773, P3= 0.849						
<b>Creatinine</b>	Mean ±SD	3.85±2.74	3.73±1.52	3.00±0.68	0.559	0.574	3.26	4.18
	Range	1.40-9.00	1.60-6.00	2.10-3.50				
<b>Post hoc</b>		P1=0.810*, P2=0.294, P3=0.381						
<b>C-reactive protein</b>	Mean ±SD	32.20±44.03	38.07±26.97	113.60±27.95	18.632	<0.001*	33.39	51.73
	Range	2.90-149.00	4.30-85.40	85.80-149.00				
<b>Post hoc</b>		P1= 0.483, P2<0.001*, P3<0.001*						
<b>eGFR</b>	Mean ±SD	24.17±14.26	22.63±11.99	22.18±3.96	0.188	0.829	20.73	26.04
	Range	6.20-56.13	10.55-50.13	19.22-27.45				
<b>Post hoc</b>		P1= 0.593, P2= 0.670, P3= 0.926						

CKD: Chronic kidney disease. Ca: Calcium. iPTH: Intact parathyroid hormone. F: ANOVA F test. \*Significant. CI: Confidence interval for Mean.

**Table [3]:** Trans-Thoracic Echocardiography of cases among serum uric acid values studied groups [n=90]

Variables		Serum uric acid values			F	P value	95% CI	
		<10 mg/dL [n=47]	10–15 mg/dL [n=34]	>15 mg/dL [n=9]			Lower	Upper
<b>EF</b>	Mean ±SD	67.45±7.58	69.47±6.58	64.67±7.86	1.787	0.174	66.40	69.46
	Range	51.00-83.00	57.00-83.00	58.00-75.00				
<b>Post hoc</b>		P1=0.218, P2=0.294, P3=0.080						
<b>IVSd</b>	Mean ±SD	11.30±2.01	11.56±2.18	11.00±2.29	0.304	0.738	10.93	11.80
	Range	8.00-15.00	9.00-16.00	8.00-13.00				
<b>Post hoc</b>		P1=0.583, P2=0.698, P3=0.480						
<b>LVPWd</b>	Mean ±SD	11.77±1.64	11.62±1.41	11.67±2.18	0.085	0.919	11.36	12.04
	Range	9.00-14.00	10.00-14.00	9.00-14.00				
<b>Post hoc</b>		P1=0.685, P2=0.867, P3=0.936						
<b>LVEDd</b>	Mean ±SD	49.70±4.73	52.97±2.63	53.33±5.22	7.426	0.001*	50.38	52.22
	Range	42.00-58.00	49.00-58.00	47.00-59.00				
<b>Post hoc</b>		P1=0.001*, P2=0.017*, P3=0.815						
<b>LVESD</b>	Mean ±SD	31.30±4.51	32.00±4.02	33.67±6.73	1.060	0.351	30.84	32.76
	Range	24.00-40.00	24.00-40.00	25.00-40.00				
<b>Post hoc</b>		P1=0.498, P2=0.159, P3=0.335						
<b>LV mass</b>	Mean ±SD	224.99±66.85	243.04±52.11	251.63±98.69	1.092	0.340	220.74	248.21
	Range	132.00-337.00	181.00-332.00	132.00-358.90				
<b>Post hoc</b>		P1=0.224, P2=0.267, P3=0.727						
<b>LVMI</b>	Mean ±SD	119.08±35.10	132.03±32.02	159.32±73.94	4.251	0.017*	119.47	136.52
	Range	67.00-179.00	98.28-197.00	73.87-244.63				
<b>Post hoc</b>		P1=0.147, P2=0.006*, P3=0.067						
<b>LAVI</b>	Mean ±SD	20.06±3.15	22.21±4.48	23.91±5.18	5.260	0.007*	20.40	22.12
	Range	15.26-28.00	17.33-31.25	17.53-29.40				
<b>Post hoc</b>		P1=0.017*, P2=0.008*, P3=0.251						
<b>MVE vel</b>	Mean ±SD	0.72±0.17	0.71±0.14	0.52±0.27	5.594	0.005*	0.66	0.73
	Range	0.34-0.95	0.43-0.87	0.34-0.88				
<b>Post hoc</b>		P1=0.716, P2=0.001*, P3=0.004*						
<b>MVA vel</b>	Mean ±SD	0.82±0.16	0.75±0.15	0.48±0.00	20.926	<0.001*	0.72	0.80
	Range	0.48-1.09	0.50-1.00	0.48-0.48				
<b>Post hoc</b>		P1=0.028*, P2<0.001*, P3<0.001*						
<b>E/A</b>	Mean ±SD	0.88±0.20	0.91±0.20	1.07±0.55	2.072	0.132	0.86	0.96
	Range	0.63-1.30	0.63-1.30	0.70-1.80				
<b>Post hoc</b>		P1=0.615, P2=0.045*, P3=0.098						
<b>e' m/s</b>	Mean ±SD	11.91±3.22	10.62±2.86	7.33±0.50	9.586	<0.001*	10.30	11.64
	Range	7.00-18.00	8.00-18.00	7.00-8.00				
<b>Post hoc</b>		P1=0.053, P2<0.001*, P3=0.004						
<b>E/e' ratio</b>	Mean ±SD	6.53±2.51	6.91±1.86	6.93±3.05	0.304	0.739	6.23	7.20
	Range	3.20-11.96	3.70-10.80	4.90-11.00				
<b>Post hoc</b>		P1=0.472, P2=0.639, P3=0.982						

EF: Ejection fraction. IVSd: Interventricular septum thickness in diastole. LVPWd: Left ventricular posterior wall thickness in diastole. LVEDd: Left ventricular end-diastolic diameter. LVESD: Left ventricular end-systolic diameter. LV: Left ventricular. LVMI: Left ventricular mass index. LAVI: Left Atrial Volume Index. MVE vel: Mitral valve flow E wave velocity. MVA vel: Mitral valve flow A wave velocity. E/A: E wave/A wave ratio. e': Peak velocity of early diastolic mitral annular motion as determined by pulsed wave Doppler. E/e': Ratio of E to E'. F: ANOVA F test. \*Significant. CI: Confidence interval for Mean.

## DISCUSSION

Left ventricular hypertrophy [LVH] and left ventricular diastolic dysfunction [LVDD] commonly occur in patients with chronic kidney disease [CKD] and are recognized as independent risk factors for future cardiovascular issues and mortality in this population [8].

In this study, serum uric acid, systolic blood pressure, and C-reactive protein levels were significantly higher in the group with levels exceeding 15 mg/dL compared to those with levels below 10 mg/dL and those between 10 and 15 mg/dL. In the research conducted by **Kim et al.** [4], patients with elevated serum uric acid [SUA] demonstrated significant differences between the two groups concerning systolic blood pressure, urinary albumin, phosphate levels, and reduced eGFR, albumin, and hemoglobin levels. Additionally, the study by **Cai et al.** [9] noted that one participant with an eGFR of less than 60 ml/min per 1.73 m<sup>2</sup> had a uric acid level that significantly placed them in the fourth quartile [Q4], implying that this parameter may serve as an indicator of kidney function for that participant. Furthermore, **Messerli et al.** [10] found that the fractional secretion of uric acid ranges from approximately 7% to 10%, indicating a direct relationship between serum uric acid levels and renal vascular resistance in individuals with essential hypertension. Hyperinsulinemia may lead to a decrease in the urinary excretion of uric acid and sodium, potentially through reduced tubular secretion, increased reabsorption, or a combination of both processes.

In our study, the left ventricular end-diastolic diameter and left atrial volume index were significantly higher in the group with uric acid levels over 15 mg/dL compared to those with levels below 10 mg/dL and between 10–15 mg/dL. Conversely, the mitral valve flow E wave velocity, A wave velocity, and peak velocity of early diastolic mitral annular motion, as assessed by pulsed wave Doppler, were significantly greater in the group with uric acid levels below 10 mg/dL than in the other two groups. In this regard, **Fujita et al.** [11] found that SUA levels were independently associated with LVH, with an odds ratio [OR] of 2.79 in a study of 116 male patients with cardiac conditions. Additionally, **Yamauchi et al.** [12] demonstrated that SUA levels were linked to LVH independently of confounding factors such as fibroblast growth factor [FGF] 23 and diuretics in cohorts of 219 females and 519 males with cardiac diseases, all of whom were not on uric acid-lowering medications.

**Zeng et al.** [13] discovered that elevated SUA levels were linked to an increased risk of LVH in patients with CKD and type 2 diabetes. **Yoshitomi et al.** [8] found that SUA levels were associated with left ventricular mass index [LVMI] and LVH in female CKD patients, but no such association was observed in male patients. Unlike these previous studies, our multivariable analysis indicated a

connection between SUA levels and LVH in CKD patients that was independent of diabetes status or sex, suggesting that SUA levels serve as an independent predictor of LVH in this population.

Uric acid is mainly linked to gout, but in recent decades, it has also been identified as a risk factor for cardiovascular diseases [CVDs] in different groups, including the general population without comorbidities as well as those with hypertension, congestive heart failure, and diabetes [14].

The exact mechanism behind LVH and LVDD in CKD patients remains unclear. LVH and LVDD are closely interconnected, with LVH and myocardial fibrosis being the primary contributors to LVDD, as they lead to increased myocardial stiffness and compromise cardiac function during diastole. In CKD, LVH occurs as a normal physiological reaction to pressure and volume overload. Factors such as prolonged pressure and volume overload, along with uremia-related issues like anemia, hyperparathyroidism, chronic inflammation, and elevated levels of FGF 23, are thought to play significant roles in the development of LVH in these patients [15].

Additionally, **Kim et al.** [4] found that the optimal cutoff value for SUA levels to predict the presence of LVDD was  $\geq 6.3$  mg/dL, showing a sensitivity of 78.4% and a specificity of 79.4%. However, when combined with other significant factors in a multivariable analysis [such as systolic blood pressure], the area under the curve [AUC] was comparable to that of SUA alone. Furthermore, the study by **Cai et al.** [9] indicated that the ROC curve demonstrated that serum uric acid is a significantly better indicator of renal function in this patient group. Nonetheless, if SUA is indeed a risk factor for renal disease progression, using baseline renal function-normalized SUA, which may better reflect the net production of uric acid, could serve as a more effective predictor of incident CKD than SUA alone.

While this study provides valuable insights into the relationship between serum uric acid levels and cardiovascular complications in chronic kidney disease [CKD] patients, there are several limitations to consider. First, the study's observational design restricts our ability to establish causal relationships between elevated serum uric acid and the observed cardiovascular outcomes. Also, the sample size may limit the generalizability of the findings, as a larger cohort could provide more robust results. Furthermore, potential confounding factors, such as medications, comorbidities, and lifestyle factors, were not comprehensively controlled for, which may have influenced the outcomes. Lastly, the cross-sectional nature of the study means that it only captures a snapshot of the participants' conditions at a single point in time, making it difficult to assess changes over the disease course. Future longitudinal

studies are needed to better understand the dynamics of serum uric acid and cardiovascular health in CKD patients.

**Conclusion:** Elevated serum uric acid levels are significantly linked to greater left ventricular hypertrophy and diastolic dysfunction in chronic kidney disease [CKD] patients who have preserved ejection fraction. Serum uric acid may contribute to the onset of cardiovascular complications in this group.

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