DOI: 10.7860/JCDR/2024/69708.19568

Original Article

Internal Medicine Section

Study of Serum Uric Acid Levels in Diabetic Kidney Disease and its Association with Left Ventricular Hypertrophy and eGFR: A Cross-sectional Study

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ABSTRACT

Introduction: Cardiovascular diseases are a major cause of death among patients with Diabetic Kidney Disease (DKD). Left Ventricular Hypertrophy (LVH) is a threatening prognostic sign and an independent risk factor for cardiovascular mortality and morbidity. A number of epidemiological studies have proven that LVH is common in patients with DKD.

Aim: To estimate the Serum Uric Acid (SUA) levels in DKD patients and its association with LVH and estimated Glomerular Filtration Rate (eGFR).

Materials and Methods: The current study was a cross-sectional study conducted at KR Hospital, Mysuru, a teritary care hospital, in Mysuru, Karnataka, India, during the period from 1st January 2020 to 31st December 2020. which included 53 patients with DKD. The demographic data, relevant investigations like Renal Function Test (RFT), SUA levels, complete haemogram, Fasting Blood Sugar (FBS), Postprandial Blood Sugar (PPBS), glycosylated haemoglobin, Liver Function Tests (LFT), urine routine, Urine Albumin Creatinine Ratio (UACR), electrocardiogram, 2D echo were done. The results were tabulated, and the patients were classified into those with high and low SUA levels. They were also evaluated for the presence of additional risk factors like hypertension and Ischaemic Heart Disease (IHD). Data obtained was analysed statistically using Statistical Packages of Social Sciences (SPSS) version 21.0 software. Mean, Standard Deviation (SD), Chi-square test, and Fischer's-exact tests were used where appropriate, with a p-value <0.05 considered statistically significant. Patients were classified into two groups, one with SUA more than 6.5 and the other with less than 6.5, as normouricaemia and hyperuricaemia, respectively.

Results: The majority of the cases were in the age group of 51-60 years, accounting for 43.4%. Out of 53 patients, males constituted 60.4% and females 30.6%, with a male-to-female ratio of 1.52:1. Total 33 patients (62.3%) were hypertensive, 32 patients (60.4%) had LVH, and 15 patients (28.3%) had IHD. Among 38 patients with SUA levels >6.5 mg/dL, the mean UACR value was higher (1807.9 mg/gm), the mean eGFR value was 32.4 mL/min/1.73 m^2, and the mean Left Ventricular Mass index (LVMI) was 117.1 g/m^2, which was statistically significant.

Conclusion: In patients with DKD, higher SUA levels were associated with significantly higher values of UACR, lower eGFR values, higher LVMI values, and an increased risk for LVH, hypertension, and IHD. However, there was no significant association between higher uric acid levels and HbA1c.

Keywords: Coronary disease, Estimated glomerular filtration rate, Hyperuricemia, Left ventricular mass index

INTRODUCTION

The rising tide of Type 2 Diabetes Mellitus (T2DM) is becoming an increasingly powerful threat to global health [1]. It is noted that diabetes is estimated to affect more than 8% of the global population, which may cover nearly more than 350 million people, which can however predicted to grow to over 550 million by 2035. Also, it has been estimated that more than 40% of people with diabetes will develop Chronic Kidney Disease (CKD), including a significant number who will develop end-stage kidney disease requiring renal replacement therapies [2].

Several prospective studies have suggested that hyperuricemia is associated with an increased risk of cardiovascular events and death in both diabetic and non diabetic individuals [3-5]. Serum uric acid (SUA), a circulating end product of purine metabolism excreted predominantly by the kidney, has various biological properties. The major pathophysiological mechanisms of uric acid-induced damage include endothelial dysfunction, activation of the Renin Angiotensin Aldosterone System (RAAS), inhibition of intrarenal nitric oxide production, increased oxidative stress, and inflammation, all of which play important roles in the pathogenesis of cardiovascular disease and kidney dysfunction [6,7]. A number of clinical studies have confirmed a positive correlation between SUA levels and LVH in patients suffering from hypertension, cardiac patients, postmenopausal women, or the general population [8,9].

The CKD patients with reduced eGFR frequently have volume retention and electrolyte imbalances that may cause abnormal cardiac function, increased LVMI, and adverse cardiac events [9]. Hyperuricemia is strongly associated with peripheral, carotid, and coronary vascular disease, the development of stroke, preeclampsia, and vascular dementia [10-13]. The relationship of uric acid with cardiovascular events is particularly strong, especially in patients at high-risk for heart disease and in women [14]. Some of the cardiovascular benefits of losartan reported in the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study [15] and for atorvastatin reported in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study [16] have also been attributed to the ability of these drugs to lower uric acid levels.

With this background information, along with various other studies correlating hyperuricemia independently with LVH, LVMI, and diabetic control [3-5], the present study is undertaken to estimate the presence of hyperuricemia in patients with T2DM and DKD, and to correlate SUA levels with LVH, LVMI, and eGFR collectively, which will help assess cardiovascular risk in the population.

MATERIALS AND METHODS

The study was a cross-sectional study conducted at KR Hospital, Mysuru, a tertiary care hospital, in Mysuru, Karnataka, India, during the period from 1st January 2020 to 31st December 2020. Based on the Institutional data from the previous year, the prevalence of DKD in T2DM was reported to be 37%.

Sample size calculation: At a 95% level of significance and a 13% allowable error (margin of error), the estimated sample size estimated to be 53. Institutional Ethical Committee clearance was obtained (MMCRI/IEC/110/2019). The participants were clearly explained the objectives of the study, and informed consent was obtained in the local language (Kannada) prior to administration of the interview schedule and informed consent was obtained from all study participants.

Inclusion and Exclusion criteria: Out of the 66 patients with DKD noted during the study period, 53 were included, and 13 were excluded as per exclusion criteria mentioned below.

Inclusion criteria included T2DM patients aged over 18 years who were diagnosed with DKD as defined by the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines in 2007. Exclusion criteria comprised patients on diuretics, uric acid-lowering drugs, or other drugs that could interfere with uric acid levels, as well as those undergoing haemodialysis or peritoneal dialysis, and individuals with other known conditions causing hyperuricemia.

Study Procedure

All participants fulfilling the inclusion criteria were interviewed as per proforma which included demographic details, chief complaints, clinical examination details, and various blood investigations {RFT including serum electrolytes, SUA, complete haemogram, FBS, PPBS, LFT}, spot UACR, and the presence or absence of LVH based on 2D echo. Patients were classified into two groups, one with SUA more than 6.5 and the other with less than 6.5 [17,18], as normouricaemia and hyperuricaemia, respectively. The diagnostic probability was based on the clinical data obtained from patient charts and the results of relevant investigations.

Data obtained from these patients were systematically recorded and analysed using a statistical package. eGFR was calculated using the Modification of Diet in Renal Disease Formula {175×(S.cr)-1.154 ×(age)-0.203×(0.72 if female)×(1.212 if African American)}.

STATISTICAL ANALYSIS

Statistical analysis was carried out SPSS version 21.0 { International Business Machines (IBM) SPSS, USA} software with regression modules installed. Descriptive analyses were reported as the mean and Standard Deviation (SD) of continuous variables. Chi-square test, Fisher's-exact test, and t-test were used to establish associations. A p-value <0.05 will be considered significant.

RESULTS

Males numbered 32 (60.4%), while females numbered 21 (39.6%), resulting in a male-to-female ratio of 1.52:1. Among 15 patients with SUA levels <6.5 mg/dL, 46.7% were in the age group of 61-70 years, followed by 40% in the age group of 51-60 years. Among 38 patients with SUA levels >6.5 mg/dL, 44.7% were in the age group of 51-60 years, followed by 28.9% in the age group of 61-70 years [Table/Fig-1].

Among 15 patients with SUA levels <6.5 mg/dL, the mean UACR value was 1181.4 mg/gm, the eGFR value was 62.86 mL/min/1.73 m^2, and the mean LVMI value was 89.6 gm/m^2. Among 38 patients with SUA levels >6.5 mg/dL, the mean UACR value was higher (1807.9 mg/gm), the mean eGFR value was 32.43 mL/min/1.73 m^2, and the mean LVMI value was 117.1 gm/m^2, which was statistically significant [Table/Fig-2,3].

Age (years)	SUA (mg/dL) <6.5 n (%)	SUA (mg/dL) >6.5 n (%)	Total
40-50	2 (13.3%)	3 (7.8%)	5
51-60	6 (40.0%)	17 (44.7%)	23
61-70	7 (46.7%)	11 (28.9.0%)	18
71-80	0 (0.0%)	7 (18.4%)	7
Total	15 (100%)	38 (100%)	53

[Table/Fig-1]: Comparison between different age groups and Serum Uric Acid (SUA) levels.

Variables	Mean
FBS	187 mg/dL
PPBS	239 mg/dL
HbA1C	8.9%
Creatinine	1.83 mg/dL
Sodium	141 meq/L
Potassium	4.8 meq/L

[Table/Fig-2]: Mean values of various parameters studied.

Comparison of the presence or absence of LVH, IHD, HTN with SUA levels: Among 38 patients with SUA levels >6.5 mg/dL, 81.6% of patients (n-31) had LVH, 36.8% (n-14) had IHD, and 71.1% (n-27) were hypertensive, all of which were statistically significant. Among 15 patients with SUA levels <6.5 mg/dL, 93.3% of patients (n-14) did not have LVH, 6.7% (n-1) had IHD, and 60% (n-9) were non hypertensive [Table/Fig-4].

	SUA (mg/dL)				
	<6.5		>6.5		
LVH*	n	%	n	%	p-value
Yes	1	6.7	31	81.6	<0.001
No	14	93.3	7	18.4	
IHD#					
Yes	1	6.7	14	36.8	0.028
No	14	93.3	24	63.2	
HTN$					
Yes	6	40	27	71.1	0.036
No	9	60	11	28.9	

[Table/Fig-4]: Comparison of presence or absence of LVH, IHD, HTN, with Serum Uric Acid (SUA) levels.
*: Left ventricular hypertrophy; #: Ischaemic heart disease; $: Hypertension; Chi-square test

Comparison between HbA1c and SUA levels: The mean HbA1c among patients with SUA <6.5 mg/dL was 9.36%. In patients with SUA >6.5 mg/dL, the mean HbA1c was 8.74%. There was no significant association between SUA and HbA1c (p-value- 0.236).

DISCUSSION

The present study was a cross-sectional study conducted to determine the SUA levels in DKD and its association with LVH and eGFR.

SUA (mg/dL)	n	Mean UACR (mg/gm)	Std. deviation	p-value	Mean eGFR (mL/min/1.73 m^2)	Std. deviation	p-value	Mean LVMI (gm/m^2)	Std. deviation	p-value
<6.5	15	1181.4	604.7	0.013	62.86	13.10	<0.001	89.6	17.17	<0.001
>6.5	38	1807.9	862.4		32.43	9.94		117.1	21.18	

[Table/Fig-3]: Comparison of UACR, eGFR and LVMI with Serum Uric Acid (SUA) levels.
t-test

Comparison of correlation between you SUA and LVMI and other studies: In the current study, the ages of subjects ranged from 40 to 80 years, with a mean age of 61.09 ± 8.53. The majority of cases were between the age group of 51-60 years, accounting for 43.4%, which is comparable to the studies done by Behradmanesh S et al., and Neupane S et al., [19,20]. In the present study, among 53 patients, males numbered 32 (60.4%) and females numbered 21 (30.6%). The male-to-female ratio in this study is 1.52:1. In a study conducted by Latif H et al., the male-to-female ratio was 0.9:1 [21], whereas study conducted by Neupane S et al., it was 1.38:1 [Table/Fig-5] [19-21].

Comparison of the correlation between SUA and LVMI with other studies. In the present study, among 38 patients with SUA levels >6.5 mg/dL, the mean LVMI value was 117.1 gm/m^2, which was statistically significant. In a retrospective study by Zeng C et al., LVMI showed a significant positive correlation with SUA (r-value=0.182, p-value<0.001) [25]. In another study conducted by Chen S et al., UA was positively correlated with LVMI (r-value=0.173, p-value<0.001) [26].

Comparison of the correlation between SUA and LVH with other studies. In the present study, among 38 patients with SUA levels >6.5 mg/dL, 81.6% patients (n-32) had LVH, which was statistically significant.

Studies	Study location	Sample size	Year of study	Mean age (years)	Male, n (%)	Female, n (%)
Present study	India	53	Jan 2020-Dec 2020	61.09±8.53	32 (60.4%)	21 (30.6%)
Latif H et al., [21]	Pakistan	200	Aug 2014-Feb 2015	48.1±10.26	97 (48.5%)	103 (51.5%)
Behradmanesh S et al., [19]	Iran	60	2011	57±8.3	26 (43.3%)	34 (56.7%)
Neupane S et al., [20]	Nepal	50	-	58.94±13.8	29 (58%)	21 (42%)

[Table/Fig-5]: Comparison of age distribution and gender distribution [19-21].

Comparison of correlation between you SUA and LVH and other studies: In the present study, among 38 patients with SUA levels >6.5 mg/dL, the mean UACR value was higher (1807.9 mg/gm), which was statistically significant when compared to subjects with SUA levels <6.5 mg/dL. In a study conducted by Suryawanshi KS et al., the mean SUA and urine microalbumin levels were significantly elevated in type 2 diabetic patients compared to healthy controls (p-value<0.001). In another study by Fukui M et al., SUA concentration was higher in patients with macroalbuminuria than in patients with Microalbuminuria (MA) or normoalbuminuria [Table/Fig-6] [21-23].

In a study conducted by Zeng C et al., there was significant increased risk of LVH with the subjects whose SUA levels > 470 µmol/L (p-value<0.008) [25]. Another study by Fujita SI et al., demonstrated that the association between SUA and LVH remained significant after adjustment for age, blood pressure, eGFR, and serum calcium phosphate metabolism-related parameters such as calcium, phosphate, intact PTH, and Fibroblast Growth Factor (FGF) 23 [27]. However, this positive association has not been confirmed in several epidemiological studies.

Studies	Study location	Sample size	Year of study	SUA (mg/dL)	UACR (mg/gm)	p-value
Present study	India	53	Jan 2020-Dec 2020	>6.5	1807.9	0.013
Suryawanshi KS et al., [22]	India	83	Jan 2019 to Jan 2020	5.95±1.65	53.34±31.94	<0.001
Fukui M et al., [23]	Japan	343	2008	5.8±1.4	>300	<0.0001
Latif H et al., [21]	Pakistan	200	Aug 2014-Feb 2015	6.99±1.01	49.82±9.56	<0.0001

[Table/Fig-6]: Comparison of association between Serum Uric Acid (SUA) and UACR with other studies [21-23].

Studies	Study location	Sample size	Year of study	SUA (mg/dL)	LVMI (g/m^2)	p-value
Present study	India	53	Jan 2020-Dec 2020	>6.5	117.1	<0.001
Zeng C et al., [25]	China	710	Jan 2009 to Jan 2015	>7.9	110.12±30.08	<0.001
Chen S et al., [26]	Taiwan	540	Jan 2007 to May 2010	9.6±1.6	193.1±45.1	<0.001

[Table/Fig-7]: Comparison of association between Serum Uric Acid (SUA) and LVMI with other studies [25,26].

In a study conducted by Latif H et al., the mean SUA level was 6.99±1.01 (mg/dL) and MA was 49.82±9.56 (mg/g), with an r value of 0.0838 showing a positive correlation. The p-value was calculated as 0.0001 [19].

Comparison of the correlation between SUA and eGFR with other studies: In the present study, among 38 patients with SUA levels >6.5 mg/dL, the mean eGFR value was 32.43 ml/min/1.73 m^2, which was statistically significant.

In another study conducted by Chang YH et al., 2,367 patients with T2D were followed up for a mean of 4.6 years. They categorised their outcomes by CKD stage as stable (47.9%), progressing (20.6%), or regressing (31.5%). The progression group had the highest (6.9±1.8 mg/dL), and the regression group had the lowest (5.4±1.5 mg/dL) baseline SUA levels. Multivariate Cox regression analyses showed that SUA >6.3 mg/dL was an independent risk factor associated with progression in CKD stage [24].

In a retrospective study conducted by Zeng C et al., a total of 435 hospitalised Chinese patients with type 2 DKD were stratified into quartiles according to SUA level. Patients with a higher SUA quartile had a significantly lower level of eGFR (p-value<0.001). The SUA level in the Spearman's rank correlation test (r-value=-0.549; p-value<0.001) was negatively associated with eGFR [25].

Studies	Study location	Sample size	Year of study	SUA (mg/dL)	LVH (%)	p-value
Present study	India	53	Jan 2020-Dec 2020	>6.5	81.6	<0.001
Zeng C et al., [25]	China	710	Jan 2009 to Jan 2015	>6.71	38.07	<0.001
Fujita SI et al., [27]	Japan	138	Jan 2012 to Dec 2012	>6.9	41.4	<0.001
Tsioufis C et al., [28]	Greece	842	1999 to 2002	4.88	36	Not significant

[Table/Fig-8]: Comparison of association between Serum Uric Acid (SUA) and LVH with other studies [25,27,28].

For example, Tsioufi SC et al., studied 842 non diabetic patients with stage I-II essential hypertension [28]. According to the Urinary Albumin Excretion (UAE), the study population was classified into those with MA and those without MA. There were 305 participants with LVH and 537 without LVH. The present study concluded that increased SUA levels are associated with MA but not with LVH in essential hypertensive subjects [28].

Comparison of the correlation between SUA and HbA1c with other studies: In the present study, the mean HbA1c among patients with SUA <6.5 mg/dL was 9.36%, and in patients with

SUA >6.5 mg/dL, the mean HbA1c was 8.74%. There was no significant association between SUA and HbA1c. Rusdiana et al., conducted a cross-sectional study among 70 patients with T2DM, which showed the mean HbA1c level to be 8.743 with an SD of 1.80. The mean uric acid level noted in the study was 6.31 with an SD of 1.58. They found no significant association between HbA1c and uric acid levels among their study subjects (p-value>0.05) [29]. In a study conducted by Sushilendu V et al., a negative correlation between SUA and HbA1c was observed in patients with T2DM [30]. Another study by Shirsath A et al., which included a total of 120 cases of T2DM, found a significant association between uric acid levels and urine albumin, serum creatinine, twenty-four-hour urinary albumin, and HbA1c levels [31].

Comparison of the correlation between SUA and hypertension: In the present study, among 38 patients with SUA>6.5 mg/dL, 27 (71.1%) of patients were hypertensive, which was statistically significant compared to subjects with SUA levels <6.5 mg/dL. In a study conducted by Shrivastav C et al., it was noted that the mean SUA level and hyperuricaemia were significantly higher in cases of newly diagnosed hypertensives compared to healthy controls [32].

Cheng W et al., observed the association between SUA concentrations and blood pressure (systolic and diastolic blood pressures) in a cohort of healthy Chinese participants. It was found that the prevalence of hypertension and higher SUA increased with age (p-value<0.001). Hypertension was more common in participants with higher SUA than in those without (38.95% vs 30.16%, p=0.02) [33].

Comparison of the correlation between SUA and IHD: In the present study, among 38 patients with SUA >6.5 mg/dL, 36.8% (n=14) had IHD, which was statistically significant when compared with patients with SUA <6.5 mg/dL.

Freedman DS et al., examined the relation between hyperuricaemia and IHD among 5,421 persons in the First National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study. The study showed a dose-response relation for mortality from IHD, as per that study, each 1-mg/dL change in uric acid (about two-thirds of SD) among women increased the rate by 1.48 (95% confidence interval 1.3-1.7). Also, women with a uric acid level ≥7 mg/dL had a 4.8-fold (95% confidence interval 1.9-12) higher rate of IHD mortality compared to women with<4 mg/dL [34]. However, another study by Culleton BF et al., studied the relation of SUA level to incident coronary heart disease and found that uric acid levels were no longer associated with coronary heart disease, death from cardiovascular disease, or death from all causes after additional adjustment for cardiovascular risk factors [35].

Limitation(s)

The sample size taken might not sufficiently powered to reflect the community. As it was a cross-sectional study, the further follow-up and progression or regression of the study parameters were not assessed.

CONCLUSION(S)

The levels of SUA were positively associated with albuminuria in patients with DKD. Similarly, higher uric acid levels were associated with higher LVMI values and lower eGFR values. Hyperuricaemia was also found to be a significant risk factor for LVH and hypertension. Hence, uric acid, being an easily accessible test, will help correlate with various cardiovascular and renal risk associations.

Acknowledgement

Authors would like to acknowledge study participants for their kind cooperation.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jan 24, 2024
- Manual Googling: Feb 27, 2024
- iThenticate Software: Apr 29, 2024 (14%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jan 19, 2024**
Date of Peer Review: **Feb 23, 2024**
Date of Acceptance: **Apr 30, 2024**
Date of Publishing: **Jun 01, 2024**