Original Article

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

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**ABSTRACT**

**Objective:** To assess the correlation of mean serum uric acid (UA) level as a predicting tool for left ventricular diastolic dysfunction (LVDD) in patients with chronic kidney disease (CKD).

**Methodology:** A cross-sectional, analytical study was conducted at the Nephrology Department, Allied Hospital, Faisalabad from March to October 2021, using non-probability consecutive sampling method. The patients aged between 20-50 years having grade 2 to 5 CKD and left ventricular ejection fraction >50% were included in this research. The blood sample was withdrawn from each participant and serum UA level was measured through the Uricostat enzimatico method by a mono-reagent technique using a Selectra ProXL device. Pulsed wave tissue Doppler echocardiography was performed using an Esaote SpA device with a 2.5-3.5 MHz transducer to assess the LVDD.

**Results**: A total of 40 cases were included with a mean age of 42.48±6.96 years. Twenty one (52.5%) were males and 19(47.5%) were females. The mean serum UA level and mean peak early diastolic velocity (EmLV) were 6.49±0.56 mg/dL and 6.45±2.85 cm/sec, respectively. The LVDD was recorded in 31(77.5%) patients. A significant negative correlation was found between mean serum UA level and LVDD in patients with CKD (r-value=-0.846, p-value=0.0001). Pearson's correlation between mean serum UA levels and LVDD in the higher age group (36-50 years) was negative (r-value=-0.8476, p-value=0.001). Similarly, the female gender had a negative correlation between mean serum UA levels and LVDD (r-value=-0.9029, p-value=0.001).

**Conclusion**: The left ventricular diastolic dysfunction in CKD patients can be predicted by elevated serum UA levels. So, uric acid can be used as a screening tool for LVDD in CKD patients.

**Keywords**: *Chronic kidney disease. Ventricular dysfunction. Uric acid.*

## INTRODUCTION

Chronic kidney disease is a significant and rapidly growing health problem with an estimated prevalence of 13.4%, globally.[1] The progression of CKD has been associated with several complications as hypertension, hyperlipidemia, anemia, hyperuricemia, hyperkalemia, mineral bone disorder, and cardiovascular disease (CVD). End-stage renal disease reduces the quality of life and has a very high mortality rate. Cardiovascular disease is the major cause of death in CKD patients. The mortality rate in CKD patients is twice the rate of the general population and more than 50% CKD patients have CVD.[2] Chronic kidney disease has a negative effect on cardiac activity and usually leads to structural and functional changes of the left ventricle (LV). The common cardiac structure abnormalities in CKD patients are decreased diastolic distensibility, impaired relaxation of LV being the characteristics of LV diastolic dysfunction, and have an independent association with increased morbidity and mortality. The LV function deterioration in CKD patients progresses predictably, with diastolic dysfunction usually preceding systolic dysfunction indicating that maintenance of diastolic function of LV is critical for prevention of cardiac failure. Diastolic dysfunction is an important pathophysiological step in the development of heart failure and is a significant focus for CVD prevention.[3] Echocardiography being a non-invasive imaging technique has been useful to assess diastolic dysfunction.[4]

Hyperuricemia is a potentially harmful medical condition occurring as a consequence of CKD and has an association with hypertension, metabolic syndrome, and CVD, making it an effective therapeutic target for CVD prevention. Uric acid is produced mainly by the liver and intestine as an end product of purine nucleotide metabolism. Hyperuricemia has a significant role as an independent predictor of poor outcome in chronic diseases such as hypertension, coronary artery disease, chronic heart failure, and CKD. However, the pathophysiology of hyperuricemia on the function of the cardiac muscles is not fully explained. The inflammation, activation of the renin-angiotensin-aldosterone system, damage to endothelial cells, and inhibition of nitric oxide secretion are some of the proposed mechanisms for the effect of hyperuricemia on the heart.[5] Uric acid can reduce nitric

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oxide (NO) production and accelerate NO degradation by the endothelial cells. Furthermore, UA and NO undergo irreversible reactions to create 6-aminouracil, further depleting the levels of NO. The negative impact of UA on cardiovascular and renal diseases could be attributed to its direct effect on inflammation, dysfunctioning of the endothelium, impaired metabolism of nitric oxide, and the activation of the reticuloendothelial system.[6]

Xanthine oxidase is an enzyme involved in the reaction of hypoxanthine and xanthine to uric acid. The increased activity of xanthine oxidase causes the release of free radicals and increases oxidative stress, having adverse effects on the activity of cardiomyocytes. The role of xanthine oxidase reductase (XOR) in the pathology of CVD has also been proposed. Excessive levels of XOR products promote inflammatory response and lead to plaque development, promoting the process of atherosclerosis and contributing to the risk of CVD.[7] Chronic kidney disease is a growing health problem and is associated with complications such as cardiovascular diseases. Hyperuricemia has been linked to poor outcome in chronic diseases. Literature regarding the correlation of mean serum uric acid levels and left ventricular diastolic dysfunction among the Pakistani population is lacking. Furthermore, there is a gap in international literature from recent times on this correlation. So, this study was planned to evaluate the application of serum uric acid as a predictive tool for left ventricular diastolic dysfunction in CKD.

## METHODOLOGY

A cross-sectional, analytical study was conducted using the non-probability consecutive sampling technique. The patients aged between 20-50 years having grade 2 to 5 CKD and left ventricular ejection fraction >50% were included in this research. The patients with cardiac anomalies such as non-sinus rhythm, LV regional or global dysfunction, history of myocardial infarction, valvular heart disease, pericardial effusion, and uncontrolled hypertension were excluded from the study. The study was conducted from March to October 2021 at the Department of Nephrology, Allied Hospital, Faisalabad, Pakistan. The sample size of 40 was calculated by using the WHO sample size calculator with 95% confidence interval, type I error as 5%, type II error as 10% and r=0.471. Each of the participants was thoroughly explained about the purpose and procedure of the study. An informed consent was acquired from each of the participants. The participants could withdraw from the study at any moment. The institutional ethical review board of Punjab Medical College, Faisalabad, Pakistan approved the study.

The participants fulfilling the criteria of participation were included after the detailed clinical history and a thorough examination. The serum sample was sent to the Pathology Department, Allied Hospital, Faisalabad for the measurement of serum UA levels. The pathologist measured the serum uric acid level by the Uricostat enzimatico method by the mono-reagent technique using a Selectra ProXL device. The normal reference range of serum uric acid level is 3.5-6 mg/dL. The serum UA levels more than 6 mg/dL were taken as high serum UA levels. Later on, participants were sent to the Cardiology Department, Allied Hospital, Faisalabad for echocardiography to assess LVDD. As per operational definition, LVDD is defined as mean peak early diastolic velocity <8 cm/sec.[8] Pulsed wave tissue Doppler echocardiography was performed using an Esaote SpA device with a 2.5-3.5 MHz transducer. The echocardiography was evaluated by the consultant cardiologist. .

## STATISTICAL ANALYSIS

The data analysis was done using the Statistical Package for the Social Sciences (SPSS) version 23. Quantitative variables were analyzed and presented as mean and standard deviation. Frequency and percentage were calculated for all qualitative variables. Pearson's correlation was utilized to find the relation between serum UA level and LV diastolic dysfunction. The effect of modifiers such as age and gender were nullified by stratification. A p-value $\leq 0.05$ was considered statistically significant.

## RESULTS

Forty patients with CKD were included in the study with the age distribution of the patients as 7(17.5%) between 20-35 years of age and 33(82.5%) between 36-50 years of age, with the mean age as 42.48±6.96 years. Twenty one (52.5%) were males and 19(47.5%) were females. The mean serum UA level was 6.49±0.56 mg/dL. The mean EmLV was 6.45±2.85 cm/sec. The left ventricular diastolic dysfunction was reported in 31(77.5%), while 9(22.5%) had normal findings of left ventricular diastolic function (Table 1).

A significant negative correlation was found between mean serum UA level and LVDD in patients with CKD (r-value=-0.846, p-value=0.0001).

Pearson's correlation between mean serum UA levels and LVDD in the higher age group (36-50 years) was negative (r-value=-0.8476, p-value=0.001). Similarly, the female gender had a negative correlation between mean serum UA levels and LVDD (r-value=-0.9029, p-value=0.001) (Table 2).

**Table 1: Study Variables of Patients Included in the Study**

| Study Variables | | Descriptive Statistics |
|---|---|---|
| **Age (Years)** | **Mean±SD** | 42.48±6.96 |
| | **20-35** | 7(17.5%) |
| | **36-50** | 33(82.5%) |
| **Gender** | **Male** | 21(52.5%) |
| | **Female** | 19(47.5%) |
| **Serum Uric Acid Level (mg/dL)** | **Mean±SD** | 6.49±0.56 |
| | **Maximum** | 7.4 |
| | **Minimum** | 5.4 |
| **Mean Peak Early Diastolic Velocity (EmLV) (cm/sec)** | **Mean±SD** | 6.45±2.85 |
| | **Maximum** | 13 |
| | **Minimum** | 3 |
| **Left Ventricular Diastolic Dysfunction (LVDD)** | **Yes** | 31(77.5%) |
| | **No** | 9(22.5%) |

**Table 2: Stratification for Mean Serum Uric Acid Level and EmLV with regards to Age and Gender**

| Variables | | Mean Serum Uric Acid (mg/dL) | Mean EmLV (cm/sec) | r** | p-value |
|---|---|---|---|---|---|
| **Age (Years)** | **20-35** | 6.43±0.64 | 6.14±2.48 | 0.8791 | 0.0001* |
| | **36-50** | 6.52±0.57 | 6.35±2.91 | -0.8476 | 0.001* |
| **Gender** | **Male** | 6.47±0.60 | 6.48±2.84 | 0.8063 | 0.001* |
| | **Female** | 6.53±0.53 | 6.42±2.95 | -0.9029 | 0.001* |

**Significant p-value*
***Pearson's Correlation*

## DISCUSSION

Chronic kidney disease is a highly prevalent disease with a high mortality rate. It is an independent as well as an important risk factor for CVD. Multiple risk factors contribute to CVD in CKD leading to endothelial dysfunction, inflammation, insulin resistance, endoplasmic reticulum & oxidative stress, and a modifiable factor that leads to this is elevated serum UA level.[9] This study was conducted to evaluate UA levels for predicting LVDD and thus helping to reduce the morbidity and mortality associated with elevated serum UA levels.

The correlation between the mean serum UA levels and LVDD indicated an inverse relationship between these two variables (r=-0.846, p-value=0.0001). The higher the serum UA levels, the lower was LV function and vice versa. Welnicki et al. reported that serum UA levels had a significant negative correlation with ejection fraction (r=-0.15).[10] Comparable results were found in other studies.[7] Furthermore, Chiu et al. reported a significant association of high serum UA levels with low left ventricular ejection fraction (p=0.001), high left ventricular mass (p <0.001), and high left atrial diameter (p <0.001).[11] The elevated levels of serum UA have been considered as an important indicator of reduced renal function and have a causative role in the development of hypertension and CVD.[12] Hyperuricemia affects the prognosis of disease in patients with congestive heart failure. The higher serum UA level has a strong association with the higher degrees of heart failure (p=0.039) and a negative Pearson's correlation with the ejection fraction (r=-0.21) (p=0.039).[13]

We found that the higher age group had a negative correlation (r=-0.8476) between serum UA levels and LVDD than the lower age groups. Yang et al. reported an independent association of serum UA with cardiovascular mortality in older population with increasing risk at extreme levels of serum UA.[14] Another study reported that the higher levels of serum UA had a strong association with CKD in the elderly being independent of other risk factors such as higher levels of blood glucose & triglycerides, hypertension, and high body mass index.[15]

In this study, a negative correlation was found between serum UA levels and LVDD in female participants as compared to males. Sun et al. found that hyperuricemia remained an independent risk factor for coronary artery disease in females of all ages (p=0.029).[16] The serum

UA had an association with metabolic syndrome. An increase in serum UA concentration by 1 mg/dL increases the risk of metabolic syndrome by 41% and 62% in males and females, respectively, ultimately increasing the prevalence of diabetes mellitus type II and CVD.[17] Huang et al. found that high serum UA levels had an association with the clustering of CVD in elderly women (odds ratio=3.850) and women are three times more likely to develop CVD than males.[18] Many epidemiological studies have reported that increased uric acid level is a risk factor for hypertension, atherosclerosis, and cardiovascular disease.[19,20]

## CONCLUSION

The elevated serum UA levels had a significant negative correlation with the LV diastolic function in CKD. Female gender and higher age group also has a negative association with serum UA levels and LVDD. The left ventricular diastolic dysfunction in CKD patients can be predicted by elevated serum UA levels. So, uric acid can be used as a screening tool for LVDD in CKD patients.

## LIMITATIONS & RECOMMENDATIONS

Our study had a few limitations. It was a single-centered study with a small sample size. Large-scale randomized controlled trials should be conducted to find an absolute relation between the serum UA levels with CVD in CKD patients. Furthermore, clinical practice should be promoted to assess and manage the serum UA levels in patients suffering from chronic diseases to further reduce the morbidity and mortality associated with it. Awareness and screening for hyperuricemia are important in reducing adverse cardiovascular events in CKD patients.

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