Journal of Research in Applied and Basic Medical Sciences 2024; 10(3): 224-232

Original Article

RABMS Journal of Research in Applied and Basic Medical Sciences

High Sensitivity C-Reactive Protein (hs-CRP) and Uric Acid as Markers of Cardiovascular Risk in Chronic Kidney Disease Patients

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Abstract

***Background & Aims*:** The link between Chronic Kidney Disease (CKD) and Cardio Vascular Disease (CVD) has long been established. Hyperuricemia and inflammatory markers such as hs-CRP are considered to be non-traditional risk factors for cardiovascular risk in CKD patients. The aim of this study was to estimate serum hs-CRP and uric acid levels in patients with chronic kidney disease along with age and sex matched healthy controls and see whether they are statistically significant or not.

Materials & Methods: In this case-control study, totally 30 cases with ages varied from 30-70 years and 30 age and sex matched controls were selected based on inclusion and exclusion criteria. Serum CRP and Uric Acid were analyzed on Beckman Coulter AU-480 fully ***automated*** analyser, by Turbidimetric end point method and Modified Trinder end point method, respectively. Qualitative data is expressed as proportion and percentage while quantitative data is expressed as mean+SD. Statistical analysis is done using Microsoft Excel sheet and Graph pad software. A *p value <0.05* is considered as statistically significant.

Results: Results show that the patients with CKD had higher levels of hs-CRP and Uric Acid than healthy controls, implying a higher risk of cardiovascular disease in this group.

Conclusion: The present study implies that regular monitoring of these biomarkers is required in CKD patients, to assess the progression of atherosclerosis and evaluate potential interventions, thereby preventing morbidity & mortality due to cardiovascular disease.

***Keywords*:** Chronic Kidney Disease, Serum hs-CRP, Serum Uric Acid

Received 18 March 2024; accepted for publication 07 May 2024

Introduction

The link between Chronic Kidney Disease (CKD) and Cardio Vascular Disease (CVD) has long been established. This association was first suggested by Richard Bright in the early 19th century and has been substantiated in the intervening years. However, the subject has been gaining more attention in recent years (1). Patients with CKD exhibit a pronounced risk for

[DOI: 10.61186/rabms.10.3.224]

cardiovascular events: 50% of all patients with CKD stages 4 to 5 have CVD and cardiovascular mortality accounts for ≈40% to 50% of all deaths in patients with advanced CKD (stage 4) as well as end-stage kidney disease (stage 5), compared with 26% in controls with normal kidney function (2). In addition to the high risk for atherosclerosis-related complications such as myocardial infarction and stroke, cardiovascular death also results from heart failure (HF) and fatal arrhythmias, particularly in advanced CKD stages (3,4). In more than 70 studies in nondialyzed subjects with CKD, correction for classical increasing age, hypertension, dyslipidemia, diabetes, smoking and obesity did not neutralize the impact of CKD on cardiovascular risk (5).

Thus, the increased incidence of CVD in CKD is only partially accounted for by the higher prevalence of traditional risk factors. This has turned the attention on the non-traditional or the 'novel' risk factors unique to CKD (6). The non-traditional or 'novel' risk factors are 'uremia specific', or at least much more common in patients with CKD than in the general population. These include albuminuria, anaemia, hyperparathyroidism, metabolic bone disease, hyperhomocysteinaemia, malnutrition, apolipoprotein isoforms, inflammation, endothelial dysfunction and oxidative stress. The various risk factors traditional and non-traditional tend to have an additive effect and hasten atherosclerosis and progression of CKD (7, 8).

From the above, it is derived that hyperuricemia and inflammatory markers such as hs-CRP are considered to be non-traditional risk factors for cardiovascular risk in CKD patients. Uric acid is the end product of purine catabolism. Many epidemiologic studies have revealed that hyperuricemia may be another potential risk factor for cardiovascular mortality in individuals with CKD (9–11). Elevated serum uric acid (SUA) is related to the development and progression of hypertension (12), stroke (13), and cardiovascular disease (14). C-reactive protein is an acute phase reactant that belongs to the protein family known as pentraxin. It is synthesized by the liver in response to cytokines such as interleukin-1, interleukin-6, tumour necrosis factor-alpha released from macrophages and adipocytes. Elevated serum C-reactive protein (CRP) levels have been shown to be linked with the development of atherosclerosis in CKD patients (15). Analysis of hs-CRP and Uric Acid in serum is relatively easy, less time consuming and also cost-effective. Hence these two markers are selected for the current study.

Many epidemiological studies are carried out throughout the world linking hs-CRP and uric acid independently with cardiovascular risk in CKD patients (16). However, such studies are limited in India. Few studies such as a population-based study of two major cities in North and South India, which found that CKD is evident in 8.7% of the adult population, are available. This study used two common cardiovascular risk scores which classified nearly a third to half of participants with CKD as high risk for experiencing a cardiovascular event (17). Besides, literature search did not yield any research articles, which involved both these biomarkers in a single study. Hence to address the above paucity, the present study is undertaken to measure serum hs-CRP and Uric Acid levels as markers of cardiovascular risk in CKD patients, attending a Tertiary Care Centre in Kakinada district of Andhra Pradesh, India. The aim of this study was to know the variations in serum hs-CRP and Uric Acid, which are the established markers of cardiovascular risk, in patients with chronic kidney disease and compare them with that of healthy controls. The objectives of the study were included estimating serum hs-CRP levels in patients with chronic kidney disease, estimating serum Uric Acid levels in patients with chronic kidney disease, comparing the above values with age and sex matched healthy controls and see whether they are statistically significant or not.

Materials & Methods

(i) Study Design: This is a cross-sectional study planned in Rangaraya Medical College/Government General Hospital, Kakinada, AP, to assess the prevalence of elevated hs-CRP and Uric Acid levels among CKD patients at a single point from April 2023 to July 2023.

[DOI: 10.61186/rabms.10.3.224]

(ii) Study Area: The study was conducted among the confirmed cases of Chronic Kidney Disease and healthy controls for whom the investigations are done in Central lab, Department of Biochemistry, Government General Hospital.

(iii) Study Period: The study is conducted for a period of 3 months from April 2023 to July 2023.

(iv) Study Subjects: A total of 60 individuals between the age group 30-70 yrs, both males & females are included in the present study. They are divided into 2 groups as follows:

Group 1: 30 cases who were confirmed cases of chronic kidney disease.

Group 2: 30 controls who were age and sex matched healthy controls.

(a) Inclusion criteria: All the individuals who have given consent/ willing to participate are included in the present study.

(b) Exclusion criteria included Individuals who did not give consent/ not willing to participate in the present study. Also individuals with any co-morbid conditions like Gout, Malignancy, Chronic infections, Acute myocardial infarction, Chronic illness like renal and cardiovascular diseases, Patients on chronic dialysis, Inflammatory conditions like SLE, RA, Smokers, and obesity were excluded from study brcause of their interfere with the study's outcomes.

(v) Ethical approval & Informed consent: Ethical approval is obtained from the Institutional Ethical Committee before the start of the study. Informed consent is obtained from the study subjects before blood sample collection.

(vi) Estimation of biochemical markers: Serum CRP and Uric Acid were analyzed on Beckman Coulter AU-480 fully automated analyser, by Turbidimetric end point method and Modified Trinder end point method respectively. Grossly hemolysed or lipemic or icteric samples were not used for analysis in the present study and are discarded. Internal quality control monitoring using the standards provided in the kit are run. Samples are analyzed only after the daily internal quality control has been passed. The values so obtained are noted in an excel sheet**.**

(vii) Statistical analysis: Qualitative data is expressed as proportion and percentage while quantitative data is expressed as mean+SD. p value was calculated using student t-test. *p value <0.05* was considered as statistically significant and p value <0.0001 was considered as extremely statistically significant. Statistical analysis was done using Microsoft Excel sheet and Graph pad software.

Results

The results of the present study are presented in Tables 1-3. The study population consisted of 30 patients with CKD (21 males, 9 females) and 30 healthy controls (19 males, 11 females). The mean age of the CKD patients was 54.27 ± 10.11 years, compared to 52.20 ± 9.53 years for the controls. Notably, serum creatinine, hs-CRP, and uric acid levels were significantly elevated in CKD patients relative to controls ($p < 0.0001$ for all comparisons), as detailed in Tables 4 and 5.

Table 1. Gender distribution of cases and control group

Category	Cases	Percentage	Controls	Percentage
Males	21	70	19	63
Females	09	30	11	37
Total	30	100	30	100

Table 2. Comparison of Age in cases and control group

Category	Range (Years)	Mean (Years)	S.D
Cases n = 30	32 – 69	54.27	± 10.11
Controls n = 30	34 – 66	52.20	± 9.53

[DOI: 10.61186/rabms.10.3.224]

Table 3. Comparison of serum Creatinine levels in cases and control group

Category	Range (mg/dl)	Mean (mg/dl)	S.D
Cases n = 30	4.2 – 12.7	7.72	± 2.31
Controls n = 30	0.5 – 1.3	0.92	± 0.22
		p < 0.0001	

Table 4. Comparison of serum hs-CRP levels in cases and control group

Category	Range (mg/L)	Mean (mg/L)	S.D
Cases n = 30	2.3 – 6.4	4.12	± 1.06
Controls n = 30	0.4 – 2.1	1.00	± 0.45
		p < 0.0001	

Table 5. Comparison of serum Uric Acid levels in cases and control group

Category	Range (mg/dl)	Mean (mg/dl)	S.D
Cases n = 30	7.1 – 11.8	8.13	± 1.17
Controls n = 30	3.7 – 7.0	5.29	± 0.90
		p < 0.0001	

Discussion

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in chronic kidney disease (CKD) patients, accounting for about 40% of hospitalizations and 50% of deaths across all CKD stages (18, 19). The CVD process likely initiates in early CKD stages, with both traditional and non-traditional risk factors contributing to its development (20-23).

CKD patients face increased cardiovascular risk due to several factors: higher prevalence of risk factors, CKD itself being an independent risk factor, and the bidirectional relationship between CVD and CKD progression (24-26). Recent guidelines consider CKD a cardiovascular risk equivalent, placing all CKD patients in the "highest risk group" for CVD development (27, 28).

Serum hs-CRP levels:

Our study shows elevated serum hs-CRP levels in CKD patients compared to healthy controls, aligning with recent research. The Modification of Diet in Renal Disease (MDRD) study found high CRP levels to be an independent CVD risk factor in CKD patients (29). However, some studies, like the Cardiovascular Health Study (30) and Irbesartan Diabetic Nephropathy Trial (31), found conflicting results, possibly due to differences in participant risk profiles.

Albert et al. (32) demonstrated hs-CRP's value in predicting cardiovascular risk, while longitudinal analyses of the MDRD Study (33) and Nurses' Health Study (34) further supported its predictive role in CKD patients.

Mechanisms of increased hs-CRP:

Inflammation plays a crucial role in atherosclerosis pathogenesis, with CRP potentially mediating key processes (35-38). In CKD patients, both traditional and CKD-specific risk factors contribute to inflammation (Cottone et al., 2008; Silverstein, 2009). The chronic, low-grade inflammation in CKD is characterized by moderate levels of inflammatory mediators (Ramirez et al., 2006; Furman et al., 2019).

Hs-CRP can bind to damaged endothelial cells, aggregate LDL, and stimulate tissue factor production, increasing cardiovascular events. It also shows an inverse association with creatinine clearance and may contribute to glomerulosclerosis (39). Kopel et al. (40) demonstrated significant vascular endothelial dysfunction in advanced CKD patients.

[DOI: 10.61186/rabms.10.3.224]

Serum Uric Acid levels:

Our study shows increased serum uric acid levels in CKD patients compared to healthy controls. This finding is consistent with several recent studies:

- Weiner et al. (41) reported uric acid as an independent predictor of cardiovascular outcomes in stages 3-5 CKD patients.
- A meta-analysis of 12 randomized controlled trials found lower CKD progression and mortality risk in patients receiving uric acid-lowering therapy (44).
- Wen et al. (45) found higher serum uric acid levels to be a risk factor for all-cause and cardiovascular mortality in a large Taiwanese cohort.
- Meta-analyses have shown associations between hyperuricemia and increased risk of cardiovascular mortality, stroke mortality, and cardiovascular events (46-49).
- Madero et al. (50) found higher uric acid levels associated with higher all-cause and cardiovascular-related mortality in CKD stages III and IV patients.

Mechanisms of increased uric acid:

Several mechanisms support the pathogenic association between higher serum uric acid levels and cardiovascular mortality risk:

- Hyperuricemia may disturb mitochondrial function, induce oxidative stress, and stimulate inflammatory responses (51-53).
- Chronically elevated uric acid levels could cause structural changes in vessel walls and contribute to endothelial dysfunction (54).
- Vascular stiffness may be one mechanism by which hyperuricemia increases CVD risk (55-59).
- Elevated uric acid levels have been associated with greater lipid content in coronary plaques and coronary artery calcification (60-63).

Study limitations include small sample size, short duration, and lack of control for confounding factors. However, this research addresses an important area by measuring two biomarkers in a single study. Future large-scale studies are needed to validate these findings.

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Conclusion

Our study demonstrates elevated levels of serum hs-CRP and uric acid in CKD patients, highlighting the importance of regular monitoring of these biomarkers. These findings suggest that:

1. Regular assessment of hs-CRP and uric acid levels in CKD patients may help evaluate the progression of atherosclerosis and guide potential interventions.
2. Early detection of increased levels of these biomarkers could enhance prompt diagnosis of cardiovascular events, potentially improving outcomes, quality of life, and reducing disease burden and hospitalization rates.
3. The results provide new insights into the relationship between hs-CRP and uric acid as easily measurable markers of cardiovascular risk in CKD patients.

While our study has limitations, including small sample size and short duration, it addresses an important area of research by measuring two biomarkers in a single study. Future large-scale observational studies and clinical trials are needed to further validate these findings and draw more generalizable conclusions.

Acknowledgments

Not declared

Ethical statement:

This study was approved by the Institutional Ethics Committee (IEC/RMC/2023/032).

Data availability:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions:

Not declared

Funding Source:

This research received no external funding.

[DOI: 10.61186/rabms.10.3.224]

Conflict of interest:

The authors declare no conflict of interest in relation to this study.

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[DOI: 10.61186/rabms.10.3.224]