

## Original Article



# Significance of Inflammatory Markers; C-reactive Protein, Hyperuricemia, and Albuminuria in type 2 Diabetes Patients

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## Authors Contribution

<sup>1</sup>Concept/research design, data collection, responsibility and is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved, <sup>3-5</sup>statistical analysis and manuscript writing, edit of manuscript and project management, <sup>6</sup>critical revision of the manuscript for important intellectual content

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## ABSTRACT

**Objective:** To determine the significance of inflammatory markers, including C-reactive protein, hyperuricemia, and albuminuria, in individuals with type 2 diabetes.

**Methodology:** This cross-sectional analytical study was done at Diabetic Clinic and Nephrology Department of Akbar Niazi Teaching Hospital, Islamabad between Jan 2023 and July 2023. Total 150 consecutive patients aged between 35 and 60 years with type 2 diabetes were enrolled in study. Participants were divided in two groups on the basis of C-reactive protein and uric acid levels. Group-A comprised individuals with type 2 diabetes and C-reactive protein levels, while Group-B included individuals with type 2 diabetes and uric acid levels. Every patient underwent necessary clinical and laboratory assessments. The measurement of C-reactive protein was conducted through a particle-enhanced immunoturbidimetric assay.

**Results:** The study population demonstrates an average age of 49.41±7.66 years. In linear regression analysis, both C-reactive protein and uric acid emerged as independently predictor the albumin to creatinine ratio include ( $\beta=0.20$ , 95% CI 0.1-0.30, and  $p=0.001$  for C-reactive protein, and  $\beta=0.20$ , 95% CI 0.1-0.30, and  $p=0.001$  for uric acid). In logistic regression, the albuminuria odd for C-reactive protein and uric acid groups was 4.05 (95% CI 2.60-9.15,  $p=0.001$ ).

**Conclusion:** In individuals with type 2 diabetes, there was an association observed between albuminuria and heightened levels of C-reactive protein and elevated uric acid levels. Additionally, there was an interactive effect on albuminuria observed between C-reactive protein and uric acid.

**Keywords:** Albuminuria, C-reactive protein, Diabetes mellitus, type 2, Hyperuricemia; Inflammation.

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## Introduction

Diabetes mellitus (DM) poses a considerable worldwide public health challenge, impacting a significant segment of the global adult population.<sup>1</sup> Statistics reveal that approximately 463 million adults worldwide are affected by diabetes, with roughly 90% of them experiencing type 2 diabetes mellitus (T2DM).<sup>2</sup> In Pakistan, recognized as the third-highest country in terms of diabetes prevalence, data from 2016, 2018, and 2019 recorded prevalence rates of 11.77%, 16.98%, and 17.1%, respectively.<sup>3</sup> As of 2022,

the International Diabetes Federation estimates that diabetes affects 26.7% of adults in Pakistan, totaling approximately 33 million cases.<sup>4</sup> This increase is expected to escalate the economic burden by 61% by the year 2030.<sup>5</sup> The high prevalence of T2DM in Pakistan can be attributed to factors such as genetic predisposition, environmental influences, low birth weight, and gestational DM.<sup>6</sup>

Complications linked to DM, including diabetic nephropathy, retinopathy, neuropathy, stroke, and

myocardial infarction (MI), substantially add to its overall burden.<sup>7</sup> Diabetic nephropathy, a prominent renal complication, entails extensive damage to kidney cells, particularly impacting the glomeruli.<sup>8</sup> Individuals diagnosed with T2DM and concurrent hyperuricemia demonstrate a more pronounced level of renal impairment compared to those solely diagnosed with T2DM.<sup>9</sup> Moreover, hyperuricemia plays a pivotal role in hastening the progression and deterioration of renal disease in patients diagnosed with T2DM, thereby exacerbating its course.<sup>10</sup>

T2DM is characterized by insulin resistance, which contributes to chronic inflammation.<sup>11</sup> Several studies have emphasized the intricate association between DM and chronic inflammation.<sup>3,7,8</sup> Chronic inflammation is thought to play a significant role in contributing to the pathogenesis of complications in DM.<sup>7</sup> Remarkably, a particular study reported a 65% incidence of elevated C-reactive protein (CRP) in individuals with T2DM, indicating a robust association.<sup>11</sup> Nevertheless, the connection between low-grade inflammation and diabetic nephropathy remains inconclusive.<sup>3</sup> On the contrary, a different study documented a 96% occurrence of elevated CRP levels in patients with T2DM and diabetic nephropathy, in contrast to 7% in those without nephropathy.<sup>12</sup> The study objective was to determine the significance of inflammatory markers, including C-reactive protein, hyperuricemia, and albuminuria, in individuals with type 2 diabetes.

## Methodology

This analytical cross-sectional study was done at Diabetic Clinic and Nephrology Department of Akbar Niazi Teaching Hospital Islamabad between Jan 2023 and July 2023. Total 150 consecutive patients with T2DM (WHO calculator was employed to estimate the sample size, with a confidence level of 95%, an incidence of 65% for CRP in diabetic patients,<sup>11</sup> and an alpha error set at 5%), patients aged between 35 and 60 years, and both genders were included. Patients who experienced acute illness within the past one week, such as infection, acute myocardial infarction (MI), malignancy, renal derangements (creatinine  $\geq 1.5$  mg/dl), and severe uncontrolled hypertension (BP  $\geq 160/100$  mmHg), were excluded. The study employed a non-probability consecutive sampling technique to include patients in the research.

T2DM was defined as fasting blood glucose  $\geq 7$  mmol/l and random levels exceeding 11 mmol/l. CRP was deemed positive or elevated when the levels surpassed 8200 ng/ml,

determined through the immunoturbidimetric test. Any patient with proteinuria exceeding 30 mg/dl in a 24-hour period was classified as a case of diabetic nephropathy. Hyperuricemia was defined as uric acid levels  $\geq 6.5$  mg/dl or 7 mg/dl in men and  $\geq 6$  mg/dl in women. The measurement of albumin to creatinine ratio (ACR) involves dividing the albumin concentration in micrograms ( $\mu$ g) by creatinine concentration in milligrams (mg). Normo-albuminuria was ACR  $\leq 30$   $\mu$ g/mg, microalbuminuria as ACR 30-300  $\mu$ g/mg, and macroalbuminuria as ACR  $\geq 300$   $\mu$ g/mg.

After getting approval from the ethics committee of the hospital and informed consent from each patient, a comprehensive history was collected. This included baseline demographic characteristics such as age and gender. Patients were questioned about symptoms like fever, sore throat, chest pain, and shortness of breath to rule out infection and MI. The blood pressure of the patients was measured. An examination of the oral cavity was conducted to check for hyperemia suggestive of infection. Additionally, an ECG was performed to rule out MI.

Blood samples were collected and sent to the pathological laboratory within the same hospital setting for random or fasting blood sugar (FBS), renal function tests (RFTs), WBC count, quantitative CRP levels (measured by enzyme-linked immunosorbent assay), and uric acid levels (analyzed with an autoanalyzer using a phosphotungstic acid reagent). Subjects were instructed to collect a urine sample for 24 hours, excluding the morning sample, and these samples were sent for protein analysis using the immunoturbidimetric test. The concentrations of urinary albumin and creatinine were measured using an autoanalyzer. All procedures were carried out by an experience consultant chemical pathologist.

Two groups (n=75, each) of patients were made, based on their CRP levels and uric acid levels. Group-A consisted of patients with T2DM and CRP levels (normal range: 0.9 to 3 mg/L), while Group-B included patients with T2DM and uric acid levels (normal range: 4.2 to 5.5 mg/dl). The study parameters, including blood sugar levels, CRP levels, and uric acid levels, were measured. Data was gathered using a structured proforma by a senior nephrologist.

SPSS v 23 was employed for comprehensive data analysis. Age, CRP, uric acid and albuminuria were presented as mean  $\pm$  SD, while frequencies and percentages were calculated for categorical variables like gender and

hypertension. Logistic regression assessed the association between CRP and uric acid levels, with odds ratios derived from a multiple logistic regression test incorporating CRP and uric acid levels. Group comparisons utilized independent t test for continuous variables, followed by post hoc test and stratification using the Bonferroni test. A probability p-value for significance was set at  $\leq 0.05$ .

## Results

One hundred and fifty patients with T2DM were enrolled and comprised into two groups (n=75, each). The study population demonstrates an average age of  $49.41 \pm 7.66$  years. Among 150 diabetic patients, 80 (53.3%) were male, and 70 (46.7%) were females. Among 150 patients, 85 (56.7%) had normo-albuminuria, 35 (23.3%) had microalbuminuria and 30 (20%) had macroalbuminuria.

The BMI mean was  $24.50 \pm 1.24$  kg/m<sup>2</sup>, and the FBS mean was  $8.83 \pm 1.25$  mmol/L. Concerning the duration of diabetes, the overall study population showed an average duration of  $8.17 \pm 5.48$  years. The systolic blood pressure (SBP) mean was  $141.12 \pm 2.67$  mmHg, and diastolic blood pressure (DBP) mean was  $79.59 \pm 2.38$  mmHg. Concerning RFTs, the average creatinine was  $1.2 \pm 0.1$  mg/dl, and the average estimated eGFR was  $88.35 \pm 2.24$  ml/min. The overall mean WBC count for infection was  $14.24 \pm 2.49 \times 10^3/\text{mm}^3$ . The demographic details within the studied population were recorded, differentiating between two distinct groups labeled as group-A and group-B. (Table I)

The independent t test was employed for comparison of uric acid and CRP levels with albuminuria in T2DM patients (Table II). The assessment indicates that increased levels of uric acid and CRP are associated with kidney nephropathy ( $p \leq 0.05$ ).

Table II shows the mean of uric acid levels and median of CRP with interquartile ranges, revealing an association between these two levels and albuminuria.

**Table-II: Statistical comparison of CRP levels and uric acid levels in both groups. (n=150)**

Variables	Group-A (n=75)	Group-B (n=75)	p-value
Uric acid levels (mg/dl)	$4.41 \pm 1.27$	$7.13 \pm 1.45$	.0001
CRP (mg/L)	4.0 (0.9-8.0)	2.5 (0.9-8.0)	.0001
Independent sample t test			

The multiple linear regression test, with ACR as the dependent variable and age, gender, BMI, SBP, DBP, hypertension, diabetes duration, eGFR, uric acid, CRP, and WBC as independent variables, it was observed that duration of diabetes, SBP, hypertension, uric acid, and CRP emerged as independent predictors of ACR. (Table III)

**Table-III: Regression analysis between the variables, (n=150)**

Variables	$\beta$	95% CI	p-value
Diabetes duration	0.04	0.02-0.06	.001
SBP	0.01	0.01-0.02	.001
Hypertension	0.40	0.05-0.70	.01
Uric acid	0.20	0.1-0.30	.001
CRP	0.20	0.1-0.30	.001
$\beta$ : beta value with 95% confidence interval			

Multiple logistic regression was employed to explore the association between CRP, uric acid, and albuminuria (Table IV). Age, gender, and CRP was found to be associated with albuminuria after adjustment the odd = 2.45 (95% CI 1.20-3.0, and  $p=0.001$ ). When considering other risk factors such as BMI, diabetes duration, SBP, DBP, hypertension, and eGFR, this association was moderately weakened after adjusting for these variables

**Table I: Descriptive statistics of patient's demographics. (n=150)**

Variables		Group-A (n=75)	Group-B (n=75)	p-value
Ages (years)	Mean $\pm$ SD	$49.43 \pm 7.29$	$49.39 \pm 7.93$	.924
Gender (frequency, %)	Male	40 (50%)	40 (50%)	1.412
	Female	35 (50%)	35 (50%)	
	Normo	40 (53.3%)	45 (60%)	
Albuminuria	Micro	20 (26.7%)	15 (20%)	.437
	Macro	15 (20%)	15 (20%)	
BMI (kg/m <sup>2</sup> )	Mean $\pm$ SD	$24.40 \pm 1.20$	$24.60 \pm 1.28$	.358
FBS (mmol/L)	Mean $\pm$ SD	$8.71 \pm 1.00$	$8.95 \pm 1.50$	.471
Diabetes duration (years)	Mean $\pm$ SD	$7.67 \pm 5.62$	$8.67 \pm 5.32$	.001
SBP (mmHg)	Mean $\pm$ SD	$138.24 \pm 2.64$	$144.0 \pm 2.7$	.0001
DBP (mmHg)	Mean $\pm$ SD	$79.99 \pm 3.29$	$79.19 \pm 1.47$	.151
Hypertension	Percentage	58.7%	60%	.178
Creatinine (mg/dl)	Mean $\pm$ SD	$1.0 \pm 0.1$	$1.4 \pm 0.2$	.0001
eGFR (ml/min)	Mean $\pm$ SD	$86.28 \pm 1.01$	$90.42 \pm 3.47$	.0001
WBC (count $\times 10^3/\text{mm}^3$ )	Mean $\pm$ SD	$13.87 \pm 1.48$	$14.61 \pm 3.5$	.0001

**Table IV: Association between CRP, hyperuricemia and albuminuria. (n=150)**

Variables	OR	95% CI	p-value
CRP	Age, gender	2.45	1.20-3.0
	Other risk factors	1.50	1.1-2.2
	With albuminuria	1.49	1.1-2.19
Uric acid	Age, gender	2.51	1.22-3.15
	Other risk factors	1.53	1.08-2.33
	With albuminuria	1.66	1.13-2.57
Combine effect on albuminuria	CRP, uric acid	4.05	2.60-9.15

(OR=1.50, 95% CI 1.1-2.2,  $p=0.002$ ). Even after adjustment, uric acid did not modify the notable association between CRP and albuminuria. However, CRP remained associated with increased odd of albuminuria = 1.49 (95% CI 1.1-2.19, and  $p=0.002$ ). A comparable statistical approach was employed to examine the association between uric acid and albuminuria. Patients in uric acid group were associated with higher risk of albuminuria after adjustment odd = 1.85 (95% CI 1.08–3.17, and  $p=0.03$ ).

## Discussion

In this study, it was observed that elevated levels of CRP and uric acid were associated with albuminuria, irrespective of factors such as age, gender, BMI, diabetes duration, hypertension, blood pressure, and eGFR. Our findings align with previous reported association of CRP, uric acid with albuminuria in T2DM patients.<sup>13-15</sup>

Additionally, we observed a previous unreported interactive impact of CRP and uric acid on albuminuria in patients with T2DM. Patients exhibiting elevated CRP and uric acid levels were notably more likely to have increased odds of albuminuria compared to those with low CRP and uric acid values, as well as patients with elevated CRP but low uric acid values or elevated uric acid but low CRP values. The observed interaction between heightened CRP and uric acid implies that the existence of subclinical inflammation may enhance the impact of elevated uric acid on albuminuria in patients with T2DM.

The association between CRP and albuminuria lacks a clear understanding of the underlying mechanism. However, it is established that polymorphisms in the CRP gene are linked to serum CRP levels.<sup>16</sup> Interestingly, studies investigating the association of CRP polymorphisms with chronic kidney disease (CKD) discovered that the CRP variant linked to CRP concentrations did not predict CKD progression. Conversely, the CRP variant that predicts CKD progression showed no association with CRP levels.<sup>17</sup>

These results suggest that CRP might serve more as an indicator of subclinical inflammation rather than being a causative factor in vascular disease and CKD. However, it's important to note that the same might not be true for diabetic nephropathy. Emerging evidence is substantiating the pathogenic significance of CRP in diabetic nephropathy.<sup>18</sup> In a study conducted by Solbu et al uric acid was unexpectedly found to be positively associated with albuminuria.<sup>19</sup> Considering that around 70% of uric acid is eliminated by the kidneys and up to 90% is reabsorbed in the kidney, it may indeed play a role in CKD, as highlighted by Dousdampanis et al.<sup>20</sup> There is evidence suggesting that uric acid may contribute to the pathology of endothelial dysfunction and kidney injury. Mild hyperuricemia has been shown to induce endothelial dysfunction and hypertension, and both of these effects were reversed by lowering uric acid levels.<sup>21,22</sup>

Overall, our study findings carry significant clinical implications. Firstly, the data suggests that both CRP and uric acid are linked to a heightened risk of albuminuria in patients with T2DM. Moreover, the presence of an interactive effect between CRP and uric acid on albuminuria has been observed. Hence, concurrently evaluating CRP and uric acid may be beneficial in predicting the risk of diabetic nephropathy and identifying patients who might benefit from treatment to prevention or late onset of kidney injury. Secondly, the study provides evidence that elevated CRP and hyperuricemia may be viable targets for intervention of T2DM.

Certainly, the cross-sectional study design constitutes a major limitation of our study. Consequently, establishing a relation between CRP, uric acid, and albuminuria in the diabetic population is not feasible. Additionally, findings from a hospital-based study might not be universally applicable. Further clarification of these relationships warrants a study of prospective cohort conducted in population-based.

## Conclusion

This study highlighted the association between subclinical chronic inflammation, assessed by CRP, and elevated uric

acid levels with albuminuria in patients with T2DM. Furthermore, an interactive impact of CRP and uric acid on albuminuria was observed. These findings provide a basis for investigating targeted treatment to decrease inflammation and lower uric acid levels to prevent and intervention of diabetic nephropathy.

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