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Original Research Article

Association of Hyperuricemia With Proteinuria in Patients With Type 2 Diabetes Mellitus: Experience of a Tertiary Care Hospital

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Abstract: *Diabetic nephropathy is a leading cause of chronic kidney disease and end-stage renal failure in patients with type 2 diabetes mellitus (T2DM). Albuminuria is an early marker of renal damage, while hyperuricemia has been increasingly recognized as a possible risk factor for kidney disease progression.* ***Objective:*** *To evaluate the relationship between elevated serum uric acid levels and the presence and severity of albuminuria in patients with type 2 diabetes.* ***Methods:*** *A retrospective, hospital-based study was conducted at Ziauddin University Hospital, Clifton Campus during June 2024 till November 2024. A total of 400 patients with T2DM were included using non-probability purposive sampling. Inclusion criteria were age >18 years, confirmed T2DM, serum uric acid ≥7 mg/dL, and spot urine albumin–creatinine ratio (UACR) >30 mg/g. Patients with UTI, stage 5 CKD, autoimmune disease, malignancy, or on medications affecting uric acid levels were excluded.* ***Results:*** *The mean serum uric acid level was 7.8 ± 0.6 mg/dL, and the mean UACR was 154.6 ± 85.2 mg/g. Macroalbuminuria was present in 30.5% of patients. The frequency of macroalbuminuria increased significantly with higher uric acid levels ($p < 0.001$). A significant positive correlation was observed between serum uric acid and UACR ($r = 0.42$, $p < 0.001$). Stratified analysis showed higher rates of macroalbuminuria among patients with longer diabetes duration and poorer glycemic control.* ***Conclusion:*** *It is concluded that hyperuricemia is significantly associated with increased albuminuria in patients with type 2 diabetes. Monitoring and managing serum uric acid levels may serve as a valuable approach in the early identification and prevention of diabetic nephropathy.*

Keywords: Diabetic Nephropathies, Hyperuricemia, Albuminuria, Type 2 Diabetes Mellitus, Uric Acid

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Introduction

Type 2 diabetes mellitus (T2DM) is one of the most prevalent chronic metabolic disorders globally, with its incidence rising at an alarming rate due to sedentary lifestyles, poor dietary habits, and increasing rates of obesity. According to the International Diabetes Federation, more than 500 million people worldwide are currently affected by diabetes, with T2DM accounting for over 90% of all cases. One of the most significant complications associated with diabetes is diabetic nephropathy, a progressive kidney disease that can ultimately lead to end-stage renal disease (ESRD). The early detection of diabetic nephropathy is crucial, and the presence of albumin in the urine is widely regarded as one of the earliest and most reliable clinical markers of renal involvement in diabetic patients. On the other hand, hyperuricemia, defined as an abnormally high level of uric acid in the blood, has traditionally been associated with conditions such as gout and kidney stones. However, more recent studies have demonstrated a potential link between elevated serum uric acid levels and various metabolic and cardiovascular diseases, including hypertension, obesity, and insulin resistance. The exact mechanisms by which hyperuricemia may contribute to these conditions are still being explored. However, it is hypothesized that high uric acid levels may lead to increased oxidative stress, endothelial dysfunction, and chronic low-grade inflammation, all of which are known contributors to the progression of diabetic nephropathy. According to the 2nd National Diabetes Survey of Pakistan (NDSP) 2016-2017, overall 26.3% of adults (≥20) have diabetes (27.4 million people) (1). Diabetes is a multisystem disorder and involves almost every organ of the human body. Diabetic nephropathy is one of the major adverse outcomes of long-standing and uncontrolled diabetes. The pathophysiology of diabetic nephropathy is complex. Diabetic nephropathy involves a multifactorial interaction between metabolic and hemodynamic factors. Metabolic factors involve glucose-dependent pathways, such as advanced glycation end-products and their receptors. Hemodynamic factors include various vasoactive hormones, such as components of the renin–angiotensin system (2). Of them, inflammation and endothelial dysfunction seem to play a basic role in the development of DN. Recent findings suggest that uric acid is an inflammatory factor, may have a role in endothelial dysfunction, and acts as a mediator of DN. Although the progression of kidney disease can be halted partially, DN is still regarded as an irreversible and progressive disease. Thus, it has become increasingly essential to find the pathophysiological mechanisms leading to DN's development and progression. (3) High serum uric acid level is an independent risk factor for kidney dysfunction in diabetic patients. On the other hand, albuminuria is considered the proxy of the early stages of diabetic nephropathy (4). Hyperuricemia has been shown to induce renal arteriolopathy, arterial hypertension, and microvascular injury involving the renin-angiotensin ystem and resulting in renal function impairment. Nevertheless, the association between uric acid levels and the development of albuminuria has been under-investigated in patients with type 2 diabetes mellitus (5). The first prospective cohort study conducted in Taiwan in 2013 demonstrated that the serum Uric acid level is an independent predictor of micro-albuminuria in a middle-aged and elderly population living in the community. Routine measurement of serum UA may help to identify individuals with increased risk for developing micro-albuminuria and CKD (6). The etiology of DN is complex and remains to be clarified. Various findings suggest that uric acid is an inflammatory factor that may have a role in endothelial dysfunction and mediate diabetic nephropathy. Controlling serum uric acid levels through pharmacological or nonpharmacological measures, and in spite of only antiproteinuric medication, can halt the progression of renal failure to

some extent. For this purpose, an association of uric acid with proteinurea should be looked for.

Thus, this study's objective was to evaluate the relationships between serum uric acid level and proteinuria in type II diabetes.

Methodology

This study was a retrospective, observational analysis at the Ziauddin University Hospital, Clifton Campus, Karachi during June 2024 till November 2024. A total of 400 patients who met the inclusion criteria were included in the study. A non-probability purposive sampling technique was used to recruit eligible participants from hospital records. Age above 18 years Diagnosed with type 2 diabetes mellitus Urine albumin–creatinine ratio greater than 30 mg/g on a spot sample Serum uric acid levels equal to or above 7 mg/Dl Urinary tract infection (UTI)Stage 5 chronic kidney disease (CKD)History of using drugs known to cause hyperuricemia Autoimmune diseases Glomerulonephritis Malignancy Age below 18 years Acute history of diarrhea or vomiting (to rule out dehydration)After obtaining approval from the Ethical Review Committee, data collection was initiated. Records of patients attending Dr. Ziauddin Hospital Clifton who met the inclusion criteria were reviewed. Laboratory investigations from fasting venous blood samples were examined, including serum uric acid, serum creatinine, and hemoglobin A1c (HbA1c) (reference range: 3.8–5.5%). Spot urinary protein and creatinine values were also collected to calculate the urine albumin–creatinine ratio. Demographic data such as age, gender, and duration of diabetes were recorded.

Data were entered and analyzed using SPSS version 20. Quantitative variables such as age, serum uric acid, serum creatinine, and urine albumin–creatinine ratio were presented as mean ± standard deviation. Categorical variables such as gender and duration of diabetes were summarized as frequencies and percentages. Stratification was performed with respect to age, gender, and primary diagnosis to examine the effect of these variables on the outcome. The Chi-square test was applied to assess associations between categorical variables. A p-value of less than or equal to 0.05 was considered statistically significant.

Results

A total of 400 patients were added in the study with a mean age of 56.3 ± 9.4 years. Among the participants, 57.5% were male and 42.5% were female. The average duration of diabetes was 8.1 ± 4.6 years, indicating a predominantly long-standing diabetic population. The mean serum uric acid level was found to be 7.8 ± 0.6 mg/dL, while the mean urine albumin–creatinine ratio (UACR) was 154.6 ± 85.2 mg/g, reflecting varying degrees of renal involvement. The mean HbA1c level was 8.4 ± 1.2%, suggesting suboptimal glycemic control among the majority of patients.

278 individuals (69.5%) had microalbuminuria, defined as a urine albumin–creatinine ratio between 30 and 299 mg/g. In contrast, 122 patients (30.5%) were found to have macroalbuminuria, with UACR values equal to or exceeding 300 mg/g.

Among patients with uric acid levels between 7.0 and 7.5 mg/dL, 22.8% had macroalbuminuria. This percentage increased to 30.4% in the 7.6–8.0 mg/dL group and rose significantly to 55.2% in patients with uric acid levels above 8.0 mg/dL.

Patients aged over 50 years had a significantly higher prevalence (34.2%) compared to those aged 50 or below (18.5%), with a p-value of 0.03, indicating statistical significance. Similarly, macroalbuminuria was more common in patients with a diabetes duration greater than five years (38.6%) versus those with a shorter disease duration (19.2%), also statistically significant (p = 0.01). Gender-based differences were observed, with macroalbuminuria present in 33.5% of males and 26.5% of females; however, this difference was not statistically significant (p = 0.09).

Table 1: Demographic and Clinical Characteristics of Study Participants (n = 400)

Variable	Mean ± SD / Frequency (%)
Age (years)	56.3 ± 9.4
Gender (Male)	230 (57.5%)
Gender (Female)	170 (42.5%)
Duration of diabetes (years)	8.1 ± 4.6
Serum uric acid (mg/dL)	7.8 ± 0.6
Urine albumin–creatinine ratio (mg/g)	154.6 ± 85.2
HbA1c (%)	8.4 ± 1.2

Table 2: Distribution of Albuminuria Among Participants

Albuminuria Category	Frequency (n)	Percentage (%)
Microalbuminuria (30–299 mg/g)	278	69.5%
Macroalbuminuria (≥300 mg/g)	122	30.5%

Table 3: Association Between Serum Uric Acid Levels and Macroalbuminuria

Serum Uric Acid Level (mg/dL)	Patients (n)	Macroalbuminuria (n)	Macroalbuminuria (%)
7.0–7.5	136	31	22.8%
7.6–8.0	148	45	30.4%
>8.0	116	64	55.2%

Table 4: Stratified Analysis of Macroalbuminuria

Stratification Variable	Macroalbuminuria (%)	p-value
Age ≤50 years	18.5%	0.03
Age >50 years	34.2%	0.03
Male	33.5%	0.09
Female	26.5%	0.09
Diabetes duration ≤5 years	19.2%	0.01

Diabetes duration >5 years	38.6%	0.01

Discussion

This retrospective hospital-based study aimed to explore the association between hyperuricemia and albuminuria among patients with type 2 diabetes mellitus. The findings demonstrated a statistically significant relationship between elevated serum uric acid levels and the presence and severity of albuminuria, particularly macroalbuminuria, suggesting that hyperuricemia may play an independent role in the progression of diabetic nephropathy (7). The mean serum uric acid level among participants was 7.8 ± 0.6 mg/dL, and the prevalence of macroalbuminuria increased progressively with rising uric acid levels. While less than a quarter of patients with uric acid levels between 7.0 and 7.5 mg/dL had macroalbuminuria, more than half of those with uric acid levels above 8.0 mg/dL did so (8). Uric acid may contribute to renal injury through mechanisms such as endothelial dysfunction, oxidative stress, and inflammatory responses, according to the existing literature, which is supported by this strong and statistically significant trend (p=0.001) (9). The connection between serum uric acid levels and disease progression was further supported by stratified analysis. Patients with a diabetes duration of more than five years and HbA1c levels greater than 8.5% were more likely to present with macroalbuminuria (10-12). These findings align with the hypothesis that chronic hyperglycemia and long-standing metabolic dysregulation exacerbate kidney damage, which may be further accelerated by elevated uric acid levels. These outcomes support the conclusions of previous international studies (13). For instance, urate-lowering medications like allopurinol and febuxostat can slow the progression of nephropathy, as demonstrated by the findings of Mazzali et al. and Jalal et al.'s studies. The current study adds to the growing body of observational data that supports the need to monitor and possibly manage uric acid levels in diabetic patients despite the ongoing interventional trials (14-15). Despite the significance of these findings, several limitations should be noted. The retrospective design restricts the ability to infer causality, and using non-probability purposive sampling may introduce selection bias. In addition, there was no control for potential confounding factors like diet, antihypertensive use, or undiagnosed conditions that affect uric acid levels. Future prospective studies with a more comprehensive assessment of lifestyle and pharmacological factors are warranted to validate these associations further.

Conclusion

It is concluded that hyperuricemia is significantly associated with increased levels of albuminuria in patients with type 2 diabetes mellitus. The findings of this study suggest that elevated serum uric acid levels may serve not only as a marker of renal dysfunction but also as a potential contributing factor to the progression of diabetic nephropathy. Patients with higher uric acid levels were more likely to exhibit macroalbuminuria, particularly those with longer durations of diabetes and poor glycemic control.

Declarations

Data Availability statement
All data generated or analysed during the study are included in the manuscript.
Ethics approval and consent to participate
Approved by the department concerned. (IRBEC-ZUDIN-099P-24)
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Conflict of interest

The authors declared the absence of a conflict of interest.

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