The Relationship Between Microalbuminuria and Serum Uric Acid Levels in Patients With Type 2 Diabetes Mellitus

Nazire Aladağ,1 Funda Müşerref Türkmen2

Objective: Increasing evidence suggests that oxidants from uric acid synthesis may cause renal dysfunction and cardiovascular diseases by inducing inflammation and endothelial dysfunction. Variations in the correlations between inflammation and albuminuria due to race and ethnicity have been noted in diabetic patients. However, studies on this topic among Turkish patients with type 2 diabetes remain limited. This study aimed to investigate the relationship between serum uric acid levels and microalbuminuria in patients with type 2 DM.

Methods: This prospective cross-sectional study included 80 patients with T2DM, divided into two groups: 40 with microalbuminuria (30–300 mg in 24-hour urine proteinuria) and 40 without (<30 mg in 24-hour urine proteinuria). Biochemical parameters were assessed through the analysis of venous blood samples, which were collected following a 12-hour fasting period during outpatient evaluations.

Results: The study population had a mean age of 57.8±11.6 years. The mean uric acid levels (4.7±1.5 vs. 4.0±1.1, P=0.036) and the mean creatinine clearance (114.6±5.8 vs. 98.1±3.4, P=0.050) were higher in the group with microalbuminuria compared to the group without. The 24-hour urinary protein levels were positively correlated with HbA1C (r=0.305, P=0.036), uric acid (r=0.308, P=0.032), and creatinine clearance (r=0.294, P=0.050).

Conclusion: Individuals with T2DM and microalbuminuria tend to display elevated levels of uric acid. Considering the potential effects of increased uric acid levels on diabetic nephropathy, end-stage renal disease, and the development of cardiovascular disease, routine monitoring of uric acid levels in T2DM patients may be important from a prognostic perspective.

INTRODUCTION

Diabetes mellitus (DM), a major health concern, is projected to impact 578 million individuals worldwide by 2030 and escalate to 700 million by 2045.[1] Diabetes is a significant metabolic disease known for causing macrovascular complications such as cardiovascular disease (CVD) and atherosclerosis, as well as microvascular complications such as nephropathy.[2] These complications are well-established factors for the increased risk of mortality in patients with type-2 DM (T2DM).[3,4] Therefore, studies concerning the pathogenesis of diabetes and its complications are gaining increased importance.

Uric acid, a product of purine metabolism, is generated through the enzymatic actions of xanthine oxidase. This process also results in the production of oxidants, which have been implicated in cardiovascular diseases and renal dysfunction.[5] This can also induce an inflammatory response, leading to organ dysfunction. Therefore, in clinical practice, uric acid can serve as a significant marker for predicting elevated levels of oxidative stress.[6] Oxidative stress can increase reactive oxygen species (ROS), leading to renal vascular endothelial damage and the production of proteinuria.[7,8] Albuminuria, defined as the presence of an excessive amount of serum protein in the urine, is a significant indicator of kidney damage, including impaired reabsorption and filtration by the kidneys.[9] On the other hand, it has been suggested that race and ethnicity could cause significant variations in the relationship between inflammation and albuminuria in patients with diabetic diseases.[10] Globally, recent studies in patients with cardiovascular or diabetic diseases have demonstrated a significant association between uric acid levels and albuminuria levels.[11-14] However, studies on this topic among Turkish patients with T2DM remain limited.

The objective of this research was to explore the associ-
ation between microalbuminuria and serum uric acid concentrations in patients with T2DM.

**MATERIALS AND METHODS**

This prospective cross-sectional investigation, carried out at the DM Clinic of Haydarpaşa Numune Training and Research Hospital between January 2006 and May 2007, was in alignment with the Helsinki Declaration and Good Clinical Practice Guidelines. This study is a specialization thesis, it was conducted with institutional approval before 2020, the ethics committee decision was not taken at that time.

The study was conducted on 80 patients with T2DM, aged between 28 and 77 years, all of whom presented to the DM outpatient clinic. Each patient was undergoing treatment with oral antidiabetic medication. Patients with secondary and type-1 DM, suspected pregnancy, and an estimated glomerular filtration rate (eGFR) less than 60 mg/dL/1.173 m² were excluded from the study. Those suspected of pregnancy were tested for beta human chorionic gonadotropin. Patients with hypertension who were using antihypertensive drugs known to affect uric acid levels (such as losartan, various diuretics including hydrochlorothiazide, furosemide, and ethacrynic acid) were also excluded from the study.

**Operational definitions**

Patients with a significant increase in urine albumin-creatinine ratio (ACR) in the range of 30-299 mg/g of creatinine or with a urine albumin excretion rate (UAE) in the range of 30-299 mg/24 hours were considered to have microalbuminuria.

**Study protocol**

The demographic and clinical data of all patients were recorded during the outpatient examination. Biochemical parameters were assessed through the analysis of venous blood samples, which were collected following a 12-hour fasting period during outpatient evaluations. The analysis of all samples was conducted in a single laboratory, utilizing a uniform methodology detailed later in the text. Patients with T2DM were categorized into two distinct groups: those with microalbuminuria (n=40) and those without (n=40). Measurements of fat mass and body fat percentage were conducted using the Tanita Body Composition Analyzer TBF-300, following a 30-minute rest period for the subjects.

**Biochemical analysis**

The Hitachi Modular autoanalyzer (Roche Diagnostics Corp., Indianapolis, IN, USA) was used for the analysis of patients’ venous blood and 24-hour urine samples. Levels of 24-hour urine protein (microalbumin turbidimetric method), hemoglobin A1C (HbA1C) (turbidimetric inhibition immunoassay, TINIA), fasting blood glucose (FBG), and lipid parameters (enzymatic colorimetric method) were measured. The determination of low-density lipoprotein cholesterol (LDL-C) was carried out employing the Friedewald formula.\(^\text{[15]}\) Creatinine clearance was determined using the Cockcroft-Gault equation. For female patients, the obtained value was adjusted by multiplying by a factor of 0.85. The formula for creatinine clearance (mL/min) is: \((140 - \text{age}) \times \text{weight} / (72 \times \text{serum creatinine level})\).\(^\text{[16]}\)

**Statistical Analysis**

All data were analyzed with MINITAB RELEASE 14 (Minitab Inc., Pennsylvania, USA). The assessment of normal distribution was conducted through the Anderson-Darling test. Numerical data were represented in terms of mean ± standard deviation. Depending on the distribution's normality, the comparison of numerical data between the two groups was conducted using either the Student’s T-test or the Mann-Whitney U test. The correlations among numerical data sets were assessed through Pearson or Spearman correlation analysis, depending on the normality of distribution. Categorical variables were displayed in the form of numbers and percentages, with group comparisons conducted through the Chi-square test. A p-value of less than 0.05 (*) was considered statistically significant for all analyses.

**RESULTS**

The study population consisted of 80 cases including 49 women (61.3%) and 31 men (38.7%), with a mean age of 57.8±11.6 years. The mean weight was higher in the group with microalbuminuria compared to the group without (89.5±12.0 vs. 75.0±12.6, \(P=0.002\)), while the mean BMI was lower (35.1±9.6 vs. 40.0±9.6, \(P=0.024\)). The mean high-density lipoprotein cholesterol (HDL-C) was lower in the group with microalbuminuria compared to the group without (40.6±8.6 vs. 47.3±9.3, \(P=0.001\)), while the mean uric acid (4.7±1.5 vs. 4.0±1.1, \(P=0.036\)) and the mean creatinine clearance (114.6±5.8 vs. 98.1±3.4, \(P=0.050\)) were higher. There were no significant variances in other demographic and clinical findings between the groups with and without microalbuminuria (Table 1).

![Figure 1. Distribution of uric acid levels in patients with type 2 diabetes mellitus based on the presence of microalbuminuria.](image-url)
The 24-hour urinary protein levels were positively correlated with HbA1C ($r=0.305$, $P=0.036$), uric acid ($r=0.308$, $P=0.032$), and creatinine clearance ($r=0.294$, $P=0.050$), whereas they showed a negative correlation with HDL-C levels ($r=-0.318$, $P=0.011$) (Table 2).

**DISCUSSION**

Even with the latest advancements in the treatment of diabetes, nephropathy continues to be a leading cause of end-stage renal disease. Increasing evidence indicates that oxidants generated in the process of uric acid synthesis contribute to the pathogenesis of renal dysfunction and the development of cardiovascular diseases by triggering inflammation and leading to endothelial dysfunction.

Moreover, studies propose that endothelial dysfunction resulting from hyperuricemia promotes the proliferation of afferent vascular smooth muscle cells and diminishes renal perfusion. This suggests that increased levels of uric acid may play a crucial role in the progression of renal damage.

Observations indicated that patients with microalbuminuria had increased uric acid levels. A study by Behradmanesh et al. suggested that higher levels of serum uric acid might significantly contribute to the development of diabetic nephropathy. In another study conducted in patients with T2DM, a positive correlation was reported between serum uric acid concentration and urinary albumin excretion. A study involving healthy Korean men demonstrated that elevated serum uric acid levels independently increased the risk of microalbuminuria development over a period of five years. Studies have shown that even mild hyperuricemia has an independent relationship with microalbumin. Furthermore, in patients with T2DM who...
have preserved renal function, an elevation in serum uric acid levels by one standard deviation is associated with a 21% increased risk of initiating chronic kidney disease.\[^{23}\] These findings are supported by a meta-analysis involving patients with T2DM, which also revealed a link between high uric acid levels and an increased risk of diabetic kidney disease.\[^{24}\] On the other hand, a Japanese two-year cohort study indicated that higher levels of serum uric acid in diabetic patients correlate with a greater risk of diabetic nephropathy worsening, characterized by a transition from microalbuminuria to albuminuria. However, the study also revealed no association between uric acid levels and the probability of progression either from normoalbuminuria to microalbuminuria or from microalbuminuria to albuminuria.\[^{25}\] An Italian 4-year cohort study identified a significant correlation between the levels of serum uric acid and the onset risk of albuminuria, specifically in instances where the estimated GFR was under 60 mL/min per 1.73 m^2.\[^{26}\] These differences between studies may be attributable to potential variations in patients’ age ranges, follow-up durations, race, and ethnic background.\[^{27}\]

A significant finding of this study was the negative correlation between serum uric acid and HDL-C levels. Several studies have demonstrated a significant relationship between serum uric acid and the lipid profile, particularly indicating a negative correlation with HDL.\[^{28-30}\] These findings are also consistent with previous studies that indicate an overlap in the pathogenesis between hyperuricemia and dyslipidemia.\[^{31,32}\] Furthermore, studies have indicated that in patients with T2DM, higher HDL-C levels are associated with a lower likelihood of microalbuminuria.\[^{33,34}\] Similarly, in this study, HDL-C levels were found to be lower in T2DM patients with microalbuminuria. The hypothesized mechanisms by which HDL-C contributes to the pathogenesis of microalbuminuria encompass the facilitation of glomerular sclerosis and renal tubular interstitial damage, in addition to the exacerbation of systemic oxidative stress consequent to augmented oxidized LDL concentrations.\[^{35,36}\]

Numerous studies have indicated that HbA1C is an independent predictor in the development of microalbuminuria.\[^{37,39}\] In this study, the observed tendency towards lower HbA1C levels in T2DM patients with microalbuminuria. This may be associated with the elevated levels of uric acid observed in these patients. Previous studies have indicated that there is a negative correlation between serum uric acid and HbA1C levels.\[^{30,40}\] The inverse transport of uric acid and glucose in the renal tubules could be responsible for these correlations.\[^{40}\]

There are notable limitations to this study. Firstly, the study was single-center with a small sample size. Secondly, the collection of uric acid levels was limited to outpatient examinations, and there was no longitudinal monitoring of uric acid levels. Therefore, the influence of uric acid on the development of diabetic nephropathy over an extended period could not be evaluated in this study. Thirdly, medications including urate-lowering, anti-diabetic, and antihypertensive drugs were not accounted for. This might limit the generalizability of the study.

**Conclusion**

In patients with T2DM, a positive correlation exists between levels of uric acid and 24-hour urinary protein. Individuals with T2DM and microalbuminuria tend to display elevated levels of uric acid. Considering the potential effects of increased uric acid levels on diabetic nephropathy, end-stage renal failure, and the development of cardiovascular disease, routine monitoring of uric acid levels in T2DM patients may be important from a prognostic perspective.

**Informed Consent**

Retrospective study.

**Peer-review**

Externally peer-reviewed.

**Authorship Contributions**


**Conflict of Interest**

None declared.

**REFERENCES**


11. Lai YJ, Chen YY, Ku PW, Chen LJ, Yen YE. Association between serum uric acid level and incidence of albuminuria in patients with type 2 diabetes mellitus: A 4.5-year cohort study. Medicine Baltimore 2021;100:e27496. [CrossRef]
28. Vaziri ND. Lipotoxicity and impaired high density lipoprotein-mediated reverse cholesterol transport in chronic kidney disease. J Ren Nutr 2010;20:335–43. [CrossRef]
33. Wei F, Chang B, Yang X, Wang Y, Chen L, Li WD. Serum uric acid levels were dynamically coupled with hemoglobin A1c in the development of type 2 diabetes. Sci Rep 2016;6:28549. [CrossRef]

Gereç ve Yöntem: Bu prospektif kesitsel çalışmaya T2DM’li 80 hasta dahil edildi ve iki gruba ayrıldı: mikroalbüminüri olan 40 hasta (24 saatlik idrar proteinürisinde 30-300 mg) ve olmayan 40 hasta (24 saatlik idrar proteinürisinde <30 mg). 12 saatlik açıklık sonrası hastalardan alınan venöz kan örneklerinin analizi ile biyokimyasal parametreler değerlendirildi.

Bulgular: Çalışma popülasyonunun yaş ortalaması 57.8±11.6 yıldı. Ortalama ürik asit (4.7±1.5 vs. 4.0±1.1, P=0.036) ve ortalama kreatinin kliresi (114.6±5.8 vs. 98.1±3.4, P=0.050) mikroalbüminüri olmayan gruba göre mikroalbuminüri olan grupta daha yüksekti. 24 saatlik idrar protein düzeyleri HbA1C (r=0.305, P=0.036), ürik asit (r=0.308, P=0.032) ve kreatinin kliresi (r=0.294, P=0.050) ile pozitif korelasyon gösterdi.

Sonuç: Mikroalbuminüri olan Tip2 DM hastaların ürik asit seviyesi daha yüksek değerdi. Artan ürik asit düzeylerinin diyabetik nefropati, son dönem böbrek yetmezliği ve kardiyovasküler hastalık gelişimi üzerindeki potansiyel etkileri göz önüne alındığında, T2DM hastalarında ürik asit düzeylerinin rutin olarak izlenmesi prognozistik açıdan önemli olabilir.

Anahtar Sözcükler: Albuminüri; diyabetik nefropati; proteinüri; ürik asit; tip 2 diyabetes mellitus.