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Is the serum uric acid (SUA) level and SUA/serum creatinine (Scr) ratio a predictive biomarker for microalbuminuria in patients with diabetes mellitus?

Mercan TAŞTEMUR[1*], Çağla ÖZDEMİR[2]

[1] *Ministry of Health, Ankara City Hospital, Geriatrics, 06800, Ankara, Turkey*

[2] *Kütahya Health Sciences University Evliya Çelebi Training and Research Hospital, Department of Family Medicine, Kütahya, Turkey.*

**Corresponding author*

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ABSTRACT

The pathogenesis of diabetic nephropathy (DN) is very complex and is still not well understood. SUA has been associated with metabolic risk in a wide range of diseases. In this study, we aimed to investigate the effect of SUA and SUA/Scr ratio on renal function using glomerular filtration rate (GFR) and microalbuminuria.

A total of 399 patients with diabetes alone, excluding other conditions that affect uric acid levels, were included in the study. Patients were divided into normoalbuminuria (n:247) and microalbuminuria (n:152) groups. SUA, SUA/Scr ratios were compared.

Female gender was 53.4% in the normoalbuminuria group and 57.9% in the microalbuminuria group. There was no significant difference in gender between the groups. In the microalbuminuria group, SUA (p=0.032), glucose (p<0.001), GGT (p=0.003), HBA1C (p<0.001), and triglycerides (p<0.001) were significantly higher, while eGFR (p<0.005), HDL (p<0.001), and vitamin D (p=0.017) were significantly lower. There was a significant negative correlation between eGFR and SUA (p<0.001) and albuminuria (p=0.004) and a significant positive correlation between eGFR and SUA/Scr ratio (p<0.001).

Serum uric acid (SUA) levels have been found to be associated with renal function in diabetes. Our study confirms this association. The metabolic and microvascular effects of SUA are widely recognized. Nevertheless, further evidence is required to clarify the relationship between SUA/Scr ratio, which accounts for renal function, and DN

Keywords: Diabetic nephropathy, microalbuminuria, serum uric acid/creatine ratio

Diyabetes Mellitus hastalarında serum ürik asit (SUA) düzeyi ve SUA/Serum kreatin (Scr) oranı, mikroalbuminüri için prediktif bir belirteç olabilir mi?'

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ÖZ

Diyabetik nefropatinin (DN) patogenezi çok karmaşıktır ve hala tam olarak anlaşılamamıştır. SUA birçok hastalıkta metabolik riskle ilişkili bulunmuştur. Bizde bu çalışmada SUA ve SUA/Scr oranının böbrek fonksiyonları üzerine etkisini glomeruler filtrasyon hızı (GFR) ve mikroalbüminüri ile araştırmayı amaçladık.

Çalışmaya sadece diyabeti olan, ürik asit düzeyini etkileyen diğer durumların dışlandığı toplam 399 hasta dahil edildi.Hastalar normoalbüminüri (n:247) ve mikroalbüminüri (n:152) grubu olarak ikiye ayrıldı. SUA, SUA/Scr oranları karşılaştırıldı.

Normoalbuminüri grubunda %53,4; mikroalbuminüri grubunda %57,9 kadın cinsiyet mevcuttu. Gruplar arasında cinsiyet açısından anlamlı farklılık yoktu. Mikroalbuminüri grubunda ürik asit (p=0,032), glukoz (p<0,001), GGT (p=0,003), HBA1C (p<0,001) ve trigliserid (p<0,001) düzeyleri anlamlı olarak yüksekti; eGFR (p<0,005), HDL (p<0,001) ve D vitamini (p=0,017)ise anlamlı olarak düşüktü. eGFR ile SUA (p<0,001) ve albuminüri ((p=0,004) arasında negatif yönlü SUA/Scr oranı(p<0,001) arasında ise pozitif yönlü anlamlı bir korelasyon izlendi.

SUA düzeyleri diyabette böbrek fonksiyonları ile ilişkili bulunmuştur. Çalışmamız bu görüşü desteklemektedir. SUA'in metabolik ve mikrovasküler etkileri iyi bilinmektedir. Ancak böbrek fonksiyonuna göre düzeltme yapan SUA/Scr oranı ile DN ilişkisini açıklayacak daha çok kanıta ihtiyaç vardır.

Anahtar sözcükler: Diyabetik nefropati, mikroalbünüri, serum ürik asit /creatin oranı

[1] *dr.tastemur@gmail.com* *https://orcid.org/ 0000-0003-0320-4095* [2] *cagla_gocen06@yahoo.com.tr* *https://orcid.org/ 0000-0002-9766-1918*

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Introduction

Diabetes Mellitus (DM) is a chronic disease with a rising occurrence caused by faults in insulin release and activity. According to 2019 data from the International Diabetes Federation, there are 463 million people with diabetes worldwide, and that number is expected to reach 700 million by 2045 [1]. The rising incidence of diabetes mellitus (DM) worldwide has a considerable effect on the healthcare system by augmenting workload and expenditures. Consequently, the battle against diabetes mellitus and its complications is of significant importance [2,3].

In addition to the treatment of hyperglycemia in diabetes, screening for complications, early diagnosis and interventions are very important in terms of preventing negative consequences and improving the patient's quality of life. Diabetic nephropathy (DN) is the most frequent microvascular complication in diabetes [4].

Given the rate of progression of end-stage renal failure requiring dialysis, diabetic nephropathy is a frequent complication that significantly diminishes the patient's quality of life and also causes substantial health expenses. DN develops in roughly one-third of patients with diabetes after a latent period of several years. The pathogenesis of DN is very complex and is still not well understood [5].

Diabetic nephropathy (DN) is a clinical condition that manifests as albuminuria, progressive reduction in glomerular filtration rate, and hypertension. Nevertheless, the indicator of established diabetic nephropathy is the presence of persistent albuminuria without any indication of concomitant retinopathy or other kidney disease 5.

The screening and diagnosis of DN still rely on albuminuria examination. Albuminuria is identified by a urinary albumin excretion rate ranging from 30-300 mg within 3 to 6 month intervals. To detect diabetic nephropathy in individuals diagnosed with type 2 diabetes, the American Diabetes Association recommends screening with microalbuminuria at the time of diagnosis and annually thereafter [5,6].

Serum uric acid is the end product of endogenous and exogenous purine metabolism. Elevated serum uric acid levels are associated with many diseases and have been linked to an increased risk of hypertension, chronic renal failure, diabetes, and cardiovascular disease. Endogenous fructose is produced through the polyol pathway in patients with diabetes. Increased fructose levels also contribute to fructose-mediated uric acid production. The relationship between high levels of SUA and the development of diabetic kidney disease has been suggested by several possible mechanisms. SUA is an inflammatory factor that may be a contributor to endothelial dysfunction. In addition, SUA stimulates vascular smooth muscle cell proliferation, angiotensin, and oxidative stress via the vascular renin-angiotensin system. According to animal studies, the fructose-uric acid axis may contribute to certain clinical manifestations of diabetic nephropathy in humans [1,7].

Several studies have demonstrated that hyperuricemia is an individual risk factor for DN. However, whether SUA is only a marker or a contributing factor for microvascular disease and nephropathy in patients with diabetes mellitus remains controversial [1].

Biomarkers are defined as characteristic factors that can be objectively measured and evaluated as indicators of normal physiological or pathological processes. A simple biomarker for diabetic nephropathy may allow for an early diagnosis of the disease. Early diagnosis and treatment will prevent progression and reduce mortality, morbidity and healthcare costs [8].

Recent studies have shown that SUA levels are an indicator of kidney damage in both diabetic and non-diabetic patients. High SUA levels have been associated with many diseases. However, the fact that SUA levels are affected by renal function is a limitation. Having standardized the degree of renal function, the search for a new biomarker that evaluates serum uric acid levels and reflects net uric acid production has begun. For this purpose, the SUA/Scr ratio was developed. Recent studies have reported that SUA/SCr is associated with metabolic changes or preserved renal function [9,10].

In our country and in many countries, the microalbuminuria level cannot be checked in primary care. However, measuring SUA and creatine levels, which are easier and more cost-effective tests, would lead to a more practical evaluation. Given the role of albuminuria in DN, which is more difficult and costly to assess, it is important to simply identify associated conditions when they cannot be studied as a test. In this study, we aimed to evaluate the relationship between SUA, SUA/SCr ratio, GFR and microalbuminuria in diabetic patients.

Material Method

The research protocol for this study was approved by the institutional review boards of Kütahya Provincial Health Directorate and Kütahya University of Health Sciences (approval number:2023/05-08, date: 25.04.2023)

The records of diabetic patients admitted to the Family Medicine Outpatient Clinic of our hospital were retrospectively analyzed. Patients over 18 years of age with type 1 and type 2 diabetes who had serum uric acid, creatine, eGFR values and albumin levels in spot urine were included in the study.

A spot urine albumin level ranging from 30 to 300 mg was classified as microalbuminuria 6.

Patients with conditions that affect serum uric acid levels and other nephropathy causes such as gout disease, hypertension diagnosis, history of malignancy, and receiving antihypertensive treatment were excluded from the study.

Statistical Analysis

SPSS version 26 (IBM®, Chicago, USA) was used for statistical analysis. Normal and abnormal distribution of the variables were analysed by Shapiro-Wilk test. Descriptive statistics were expressed as mean and standard deviation in numerical data showing normal distribution, median (minimum-maximum) in data showing abnormal distribution, number and percentage in nominal data. "Student's T-test" and "One-way ANOVA" were used to analyse numerical variables showing normal distribution, and "Mann-Whitney U" test was used to analyse variables not showing normal distribution. Nominal data were compared using "Chi-square analysis". A p value below 0.05 was considered significant in statistical analyses.

Results

A total of 399 patients were included in the study. Patients were divided into 2 groups according to albuminuria level. The mean age was 53.77±11.94 years in the normoalbuminuria group and 54.69±13.16 years in the microalbuminuria group. No significant difference was observed between the groups in terms of age. Female gender was 53.4% in the normoalbuminuria group and 57.9% in the microalbuminuria group. There was no significant difference between the groups in terms of gender. In the microalbuminuria group, uric acid (p=0.032), glucose (p<0.001), GGT (p=0.003), HBA1C (p<0.001) and triglyceride (p<0.001) levels were significantly higher; eGFR (p<0.005), HDL (p<0.001) and vitamin D (p=0.017) were significantly lower. There was no significant difference between the groups in terms of other laboratory parameters.

The distribution and analysis of demographic characteristics and laboratory parameters between the groups are summarised in Table 1.

In the correlation analysis, a significant negative correlation was found between age and SUA/Scr ratio (p=0.003) and eGFR (p<0.001). A significant negative correlation was observed between eGFR and uric acid (p<0.001) and albuminuria ((p=0.004) and a significant positive correlation was observed between SUA/Scr ratio (p<0.001) (Table 2).

Table 1. Comparison of demographic characteristics and laboratory parameters between groups			
	Normoalbuminuria (N=247)	**Microalbuminuria (N=152)**	**p value**
Age*	53,77±11,94	54,69±13,16	0,357¥
Gender, Female***	132 (53,4)	88 (57,9)	0,385¥¥¥
Serum Uric acid (mg/dl)**	4,40 (1,5-33)	4,9 (1,5-12,1)	***0,032¥¥***
Serum Creatinine (µmol/L)**	0,89 (0,44-1,89)	0,89 (0,47-5,39)	0,280¥¥
SUA/Scr**	5,13 (1,9-45,21)	4,93 (0,04-16,38)	0,946¥¥
GFR (ml/dk/1,73m^2)**	86 (19-132)	80 (8-144)	***0,005¥¥***
Glucose (mg/dl)**	151 (53-499)	177 (73-444)	***<0,001¥¥***
ALT (U/L)**	19 (5-137)	19 (8-335)	0,621¥¥
GGT (U/L)**	25 (7-351)	29 (11-306)	***0,003¥¥***
Hemoglobin (g/dl)**	14 (9-18,7)	14,1 (3,6-18,1)	0,386¥¥
HBA1C**	7,7 (5,1-15,7)	9 (5-15,2)	***<0,001¥¥***
Triglyceride (mg/dl)**	143 (22-565)	171 (37-734)	***<0,001¥¥***
HDL (mg/dl)**	47 (20-165)	42,5 (17-70)	***0,001¥¥***
LDL (mg/dl)**	117 (31-250)	122 (5-255)	0,575
Total cholesterol (mg/dl)**	195 (83-338)	201 (83-361)	0,390
Vitamin D (µg/L)**	14 (1-149)	11,91 (1,82-35)	***0,017¥¥***

*Mean±sd;**Median (min-max);***N(%).¥Independent Groups T Test; ¥¥Man Whitney U Test; ¥¥¥Ki-square test. SUA/Scr: Serum uric acid/Serum creatinine GFR: Glomerular Filtration Rate; ALT:Alanin Amino Transferaz; GGT: Gama Glutamil Transferaz;HBA1C: Hemoglobin A1C;HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein.

Table 2. Correlation analysis between age and other laboratory parameters					
		Age	**Uric acid**	**SUA/Scr**	**eGFR**
Uric acid*	rho	0,014	-		
	p	0,777	-		
SUA/Scr*	rho	-0,147	0,621	-	
	p	***0,003***	***<0,001***	-	
eGFR*	rho	-0,494	-0,351	0,249	-
	p	***<0,001***	***<0,001***	***<0,001***	-
Albuminüria*	rho	0,078	0,090	-0,031	-0,146
	p	0,120	0,073	0,541	***0,004***

Discussion

Diabetic nephropathy is one of the leading causes of end-stage renal disease worldwide. Many studies have been conducted on the prevention and treatment of this important complication of diabetes. Considering the rising prevalence of DN, the present screening methods or tests for determining DN risk seem deficient. It is also important to introduce new biomarkers other than eGFR and microalbuminuria. In our study, we found a significant negative correlation between eGFR and uric acid and albuminuria, and a significant positive correlation with the SUA/Scr ratio. We also found that SUA level was significantly higher in the microalbuminuric patient group. There are many studies showing the association of SUA with diabetic kidney disease 1,11-13. However, studies investigating the SUA/Scr ratio are limited 14. Again, SUA levels have mostly been compared with eGFR levels, and there are relatively few studies with albuminuria 15-17.

Hyperuricemia is associated with worsening eGFR, albuminuria, chronic kidney disease and renal failure, according to Sharma's meta-analysis. PMID: 34104231. Hovind et al. also found that high normal SUA levels were associated with the incidence of diabetic renal failure in 277 newly diagnosed type 1 DM patients 18.

In contrast, Hayashino et al. found no association between SUA levels and eGFR decline or development of albuminuria, probably due to the heterogeneity of baseline eGFR and the short follow-up period of 1.8 years 19.

Two studies were found in the literature which evaluated the SUA/Scr ratio and the renal function in diabetic patients. Among these, Kawamato et al. used eGFR as an indicator of renal function and showed that the SUA/Scr ratio at baseline was independently and significantly associated with future decline in renal function 14.

The second study was conducted by Chen et al. In this retrospective study, SUA/Scr was found to be an independent risk factor for diabetic kidney disease in patients with type 2 diabetes, and it was emphasised that it may be helpful in detecting normoalbuminuric diabetic kidney disease 20.

In our study, we found a significant correlation between the SUA/Scr ratio and the eGFR, but not between the SUA/Scr ratio and microalbuminuria. This suggests that the metabolic effects of SUA levels may be influenced by different parameters after adjustment for renal function.

Decreases in eGFR without albuminuria are often reported in patients with diabetes. In a study by Qin et al, high SUA was shown to reduce eGFR even in people with diabetes without albuminuria 21,22. In our study, we did not find an association between microalbuminuria and SUA level and SUA/Scr ratio, but we did find a significant association with eGFR. This is in support of the study by Qin et al. However, the different results suggest that more research is needed on this topic.

Limitations:

Although this study only included a sample group with diabetes and excluded other comorbidities that may affect renal function, we had important limitations. Firstly, the retrospective nature of the study, the relatively small number of the microalbuminuria group and the use of spot urine examination for the evaluation of microalbuminuria can be counted as important limitations.

Conclusion

Considering the metabolic effects of SUA and especially its microvascular effects, we think that its effect on the complications of diabetes should be examined in more detail. The presence of studies suggesting that only strict glycaemic control is not sufficient in the progression of diabetes and development of complications supports our opinion 23. SUA/Scr ratio may be a more valuable biomarker that corrects for renal function. However, studies in DN are insufficient. We think that prospective larger scale studies are needed.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interst with respect to the research, authorship, and/or puplication of this article.

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