Araştırma Makalesi (Research Article)

Kronik Böbrek Yetmezliğinde Serum Ürik Asit Düzeyleri ve İlişkili Faktörler

Serum Uric Acid Levels and Related Factors in Chronic Kidney Disease

Can SEVINC[1], Gulay YILMAZ[2], Ozge TIMUR[3]

[1]Atatürk University, Faculty of Medicine, Department of Internal Medicine, Division of Nephrology, Erzurum, Turkey

[2]Acibadem International Hospital, Department of Nephrology, Istanbul Turkey

[3]Health Sciences University, Erzurum Regional Training and Research Hospital, Department of Internal Medicine, Erzurum, Turkey

Özet

Amaç: Pürin metabolizmasının son ürünü olan ürik asit (ÜA), hipertansiyon, iskemik kalp ve serebrovasküler hastalıklar, bazı metabolik sendromlar ve kronik böbrek yetmezliği (KBY) ile ilişkilendirilmiştir. Çalışmamızda, KBY tanısı alan hastalarda ÜA düzeylerini ölçmeyi ve sonuçların diğer faktörlerle ilişkisini göstermeyi amaçladık.

Gereç ve Yöntemler: KBY tanılı 270 hastanın verileri retrospektif olarak tarandı. Hastalar glomerular filtrasyon hızına (GFH) göre iki gruba ayrıldı. GFH ≥60ml/dk grup 1, GFH <60ml/dk grup 2 olarak adlandırıldı. Değerlendirilen diğer parametreler; demografik veriler, sistolik-diyastolik kan basıncı, ortalama arter basıncı, üre, kreatinin, ürik asit, lökosit, NLO, CRP, albumin, 24 saatlik idrarda protein ve mikroalbumin atılımıdır. İki grup arasında tüm bu parametreler ve bunların ÜA ile korelasyonunu karşılaştırdık.

Bulgular: Yaş ve cinsiyet gibi demografik verilerde istatistiksel olarak anlamlı farklılık saptanmadı. Diyastolik kan basıncı iki grup arasında anlamlı olarak fark gösterdi ancak farklı ÜA değerlerinde istatistiksel anlamlı farklılık izlenmedi. ÜA değerleri iki grup arasında anlamlı olarak farklı bulundu. Lökosit, NLO, CRP gibi inflamasyon göstergeleri, proteinüri ve mikroalbuminüri değerleri arasında istatistiksel olarak anlamlı fark saptandı.

Sonuç: KBY hastalarında artmış serum ÜA seviyeleri proteinüri, mikroalbüminüri, inflamasyon ve diyastolik kan basıncı ile doğrudan ilişkilidir. Bu nedenle, serum ÜA düzeylerinin bu faktörler üzerindeki etkisi göz önüne alındığında, ana terapötik hedeflerimizden biri serum ÜA düzeylerini düşürmek olmalıdır.

Anahtar Kelimeler: Kronik böbrek yetmezliği, Ürik asit, İnflamasyon

Abstract

Objective: The end product of purine metabolism, uric acid (UA), excreted mainly by the kidneys through tubular transporters is associated with hypertension, ischemic heart disease, cerebrovascular disease, metabolic syndrome, gout, chronic and acute kidney disease (CKD). Accumulating evidence suggests that hyperuricemia is not only a result but also a risk factor for CKD. UA levels are increasing since the early stages of CKD and elevated UA levels are associated with cardiovascular morbidity and mortality. In this study, we aimed to quantify UA levels in patients diagnosed with CKD and to correlate results with the other associated factors.

Material and Methods: In this study 270 patients diagnosed with CKD was screened. Two groups assessed; these were the group-1 with the glomerular filtration rate (eGFR) 60 ml/min1.73m2 or below and the group-2 with the eGFR above 60 ml/min. Demographic characteristics, systolic-diastolic blood pressure (SBP, DBP), mean arterial pressure (MAP), urea, creatinine, UA, leukocyte count, neutrophil-lymphocyte ratio (NLR), C-reactive protein (CRP), albumin, proteinuria and microalbuminuria in 24-hour urine were determined. Between the two groups we compared all these parameters statistically and their correlation with the serum UA.

Results: Demographic datas such as age and gender was found statistically insignificant. There was significant difference in means of DBP between the two groups. Mean serum UA showed statistically significant difference. NLR, CRP, albumin, proteinuria and microalbuminuria also showed statistically significant difference between the two groups.

Conclusion: Increased serum UA levels in CKD patients is directly associated with proteinuria, microalbuminuria, inflammation and DBP. Therefore, considering the effect of increased the serum UA levels on these factors, our one of the main therapeutic target should aim to decrease the serum UA levels.

Key words: Chronic kidney disease, Uric acid, Inflammation

Yazışma Adresi: Özge TİMUR, Sağlık Bilimleri Üniversitesi Erzurum Bölge Eğitim ve Araştırma Hastanesi, İç Hastalıkları Kliniği, Erzurum, Türkiye,

Telefon: +90 505 8574627, Mail: ozgetimur@yahoo.com

ORCID No (Sırasıyla): 0000-0002-4069-9181, 0000-0001-6565-8063, 0000-0002-7296-5536

Geliş tarihi: 3.08.2020

Kabul tarihi: 23.12.2020

DOI: 10.17517/ ksutfd.775747

INTRODUCTION

Chronic kidney disease (CKD) is an important public health problem with high morbidity-mortality rate and high treatment costs. Hypertension, proteinuria and diabetes are well known risk factors for development and progression of CKD. Although chronic kidney disease is not reversible the progression of CKD can be preventable by well identifying and avoiding risk factors.

The end product of purine metabolism, uric acid (UA), excreted mainly by the kidneys through tubular transporters is associated with hypertension, ischemic heart disease, cerebrovascular disease, metabolic syndrome, gout, chronic and acute kidney disease. Decrease in the glomerular filtration rate is accompanied by retention of uric acid. Hyperuricemia has been considered to be associated with adverse outcomes in CKD due to reduced glomerular filtration rate. Accumulating evidence suggests that hyperuricemia is not only a result but also a risk factor for CKD. UA levels are increasing since the early stages of CKD and elevated UA levels are associated with cardiovascular morbidity and mortality (1). The leading cause of cardiovascular morbidity and mortality is the endothelial dysfunction as a result of inflammation which also accelerates atherosclerosis formation. Recently a close relationship between uric acid and oxidative stress has been highlighted Several studies have shown the rapid formation of renal fibrosis in patients with high levels of UA which leaded more common occurance of end stage renal disease in return (2). In this study, we aimed to investigate the relationship between serum UA levels and other factors such as systolic-diastolic blood pressure (SBP, DBP), mean arterial pressure (MAP), urea, creatinine, uric acid (UA), leukocyte count, neutrophil-lymphocyte ratio (NLR), C-reactive protein (CRP), albumin causing adverse events and their contribution to morbidity and mortality in CKD patients.

MATERIAL and METHODS

In our study, 270 CKD patients were screened retrospectively. The study was planned according to the principles of the Helsinki Declaration. Ethics Committee of Erzurum Region Training and Research Hospital approved the study design. The study group consisted of patients aged 15-65 years, body mass index <35 kg/m^2, eGFR 15-60 ml/min/1.73m^2. Patients do not have diabetes, malignancy, cerebrovascular disease and acute health problems. Control group was established from 91 patients with eGFR values above 60 ml/min/1.73m^2. The eGFR values was calculated by the MDRD formulation. Two groups were formed according to EGFR; these were Group I with an eGFR of 60 ml / min or less and Group II with an eGFR greater than 60 ml / min. Demographic parameters of the groups were determined. Demographic characteristics; systolic-diastolic blood pressure (SBP, DBP), mean arterial pressure (MAP), urea, creatinine, uric acid (UA), leukocyte count, neutrophil-lymphocyte ratio (NLR), C-reactive protein (CRP), albumin in the serum and urine, microalbuminuria in 24-hour urine. Between the two groups compared each of the parameters previously mentioned. Additionally we investigated their correlation with the serum uric acid level. SPSS for Windows version 20 was used for statistical analysis. Descriptive statistics were summarized as mean ± standard deviation or median for continuous variables. For comparison of collected datas with a reference probability distribution and two groups with each other, we applied Kolmogorov - Smirnov testing, Student's t test was used to evaluate the differences between the two groups' data when the test statistic would follow a normal distribution. Mann Whitney u test was used for variables that did not show normal distribution. The chi-squared test was used to determine whether there is a significant difference between the expected frequencies and the observed frequencies in one or more categories. Pearson's chi-squared test analysed frequency distribution of variables consistent with a normal distribution. Spearman correlation test was chosen for abnormal distribution. $p < 0.05$ considered as statistically significant.

RESULTS

The mean age of patients in group-1 49.6±10.3 years, the mean age of the patients in group-2 47.9±13.0 years and there is no statistically significant difference between groups. 57.8 % of patients in group-1 female, 58.2% of patients in group-2 were women and there was no statistically significant difference between groups. Demographic and biochemical values of the study groups are shown in **Table 1.**

There was no statistically significant difference between the mean SBP value of the patients in group-1 and group-2 ($p = 0.24$). Statistically significant difference in mean DBP values was observed between the two groups ($p=0.024$). When group 1 with serum creatinine value of 2.5 ± 1.3 mg / dl and group 2 with creatinine value of 0.8 ± 0.2 mg / dl were compared, a statistically significant difference was found ($p<0.001$).

Mean uric acid value of the patients in group-1 was 6.9±1.3, mean uric acid value of the patients in group-2 was 5.3±1.5 and there was a statistically significant difference between both groups ($p<0.001$). Leukocyte count, NLR, CRP, albumin, proteinuria and microalbuminuria also showed statistically significant difference between the two groups (p values respectively 0.004, <0.001, 0.04, <0.001, <0.001, <0.001).

Multiple regression analysis was conducted to identify the factors significantly associated with the UA. Age ($p=0.04$, $r=0.16$), proteinuria ($p<0.01$, $r=0.4$), microalbuminuria ($p<0.01$, $r=0.62$), creatinine ($p<0.01$, $r=0.68$), CRP ($p<0.01$, $r=0.23$), NLO ($p<0.01$, $r=0.22$), SBP ($p<0.01$, $r=0.23$), DBP ($p<0.01$, $r=0.18$), BMI ($p< 0.01$, $r=0.25$) showed a positive linear relationship between UA levels. Only eGFR ($p<0.01$, $r=-0.57$) showed negative linear relationship. UA in multiple relationships with other parameters shown in **Table 2** and and **Figure 1.**

Table 1. Demographic and biochemical values of the study groups

Values	Group-1 (eGFR<60 ml/min) (n=90)	Group-2 (eGFR>60 ml/min) (n=91)	p
Age (years)	49.6±10.3	47.9±13.0	0.06
Gender (% female)	57.8	58.2	0.95
SBP (mmHg)	130 [IQR:118.75-140]	120 [IQR:120-130]	0.24
DBP (mmHg)	80 [IQR:70-90]	80 [IQR:70-85]	0.024
Creatinine (mg/dl)	2.5±1.3	0.8±0.2	<0.001
Uric Acid (mg/dl)	6.9±1.3	5.3±1.5	<0.001
Leukocyte count (103/µl)	8±2.5	7±1.8	4
NLR *	2.3[IQR:1.7-3.3]	1.8[IQR:1.5-2.4]	<0.001
Albümin (g/dl) *	4.4[IQR:4.2-4.6]	4.6[IQR:4.2-4.8]	0.04
CRP *	0.4[IQR:0.3-0.9]	0.3[IQR:0.2-0.5]	<0.001
24 Hours UPE (mg/day) *	706.5 [IQR:148.9-1867]	93.5 [IQR:53.2-156.6]	<0.001
24 Hours UAE (mg/day) *	316.3 [IQR:13.7-1200.5]	9.6 [IQR:2.7-47.9]	<0.001

SBP; Systolic Blood Pressure, DBP; Diastolic Blood Pressure, leukocyte count; White Blood Cell, NLR; Neutrophil-Lymphocyte Ratio, CRP; C-Reactive Protein, UPE; Urinary Protein Excretion, UAE; Urinary Albumin Excretion

*: Data were compared by Mann -Whitney U test. It is expressed as median and IQR.

Table 2. Uric acid in multiple relationships with other parameters

Values	p	r
Age (years)	0.04	0.16
eGFR (ml/min)	<0.01	-0.57
24 Hours UPE (mg/day)	<0.01	0.4
24 Hours UAE (mg/day)	<0.01	0.62
Creatinine (mg/dl)	<0.01	0.68
CRP	<0.01	0.23
NLR	<0.01	0.22
SBP (mmHg)	<0.01	0.23
DBP (mmHg)	<0.01	0.18
BMI (kg/m^2)	<0.01	0.25

eGFR; Glomerular Filtration Rate, SBP; Systolic Blood Pressure, DBP; Diastolic Blood Pressure, NLR; Neutrophil-Lymphocyte Ratio, CRP; C-Reactive Protein, UPE; Urinary Protein Excretion, UAE; Urinary Albumin Excretion, BMI; Body Mass Index

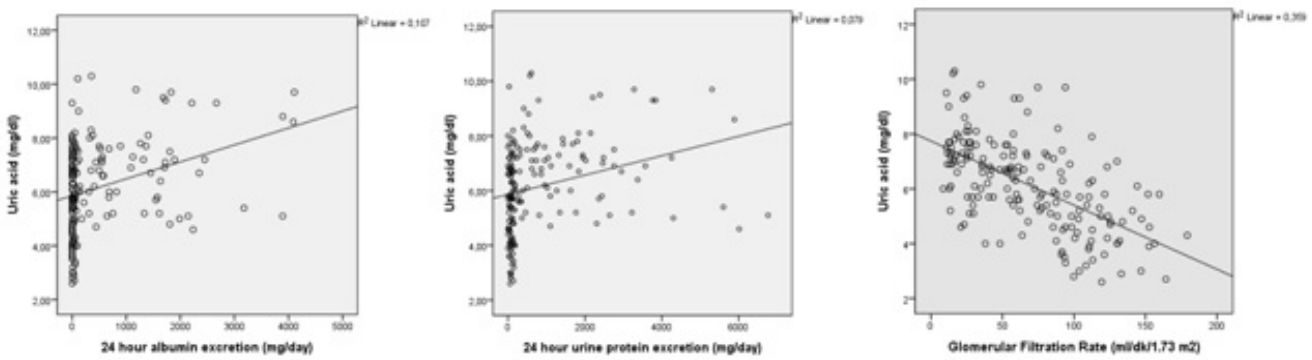

Figure 1. Uric acid in multiple relationships with other parameters

The patients were divided into two groups as those with UA >7.5 mg / dl and with UA<7.5 mg / dl. There was no statistically significant difference between the two groups in terms of age, gender, CRP, SBP and DBP (p>0.05). A statistically significant difference was detected between the two groups in terms of creatinine, leukocyte count, NLR, albumin, protein excretion in 24-hour urine and albumin excretion in 24-hour urine (p<0.05).

Table 3. Comparison of variables according to uric acid value

	UA>7.5mg/dl) (n=44)	UA<7.5mg/dl) (n=135)	p
Age (years)	47.4±10.7	46.73±11.8	0.736
Gender (% female)	50	60	0.4
SBP (mmHg*)	130 [IQR:120-133.7]	120 [IQR:120-140]	0.459
DBP (mmHg*)	80 [IQR:71.2-90]	80 [IQR:70-90]	0.197
Creatinine* (mg/dl)	2[IQR:1.2-3.4]	1[IQR:1.5-0.7]	<0.001
Leukocyte count (103/µl)	7,04[IQR:5.97-9.86]	7.01[IQR:5.87-8.65]	<0.001
NLR*	253[IQR:1.8-3.3]	1.9[IQR:1.5-2.6]	<0.001
Albumin* (g/dL)	4.25[IQR:3.95-4.60]	4.4[IQR:4.2-4.7]	0.002
CRP*	0.4[IQR:0.3-0.9]	0.4[IQR:0.2-0.6]	226
24 Hours UPE* (mg/day)	746.4 [IQR:263.35-2116.66]	128.1 [IQR:69.0-621.0]	<0.001
24 Hours UAE* (mg/day)	509.05 [IQR:42.47-1714.05]	18.45 [IQR:4.1-176]	<0.001

*: Data were compared by Mann -Whitney U test. It is expressed as median and IQR.

DISCUSSION

The increased serum UA level which is also one of the risk factor for coronary artery disease is caused by decreased glomerular filtration rate as well as its reduced tubular secretion. The serum UA level rises as a result of renal function deficiency and it causes progression of disease itself. In our study, we found statistically significant difference of serum UA levels between the two groups categorized according to eGFR. In addition, a statistically significant difference was observed in the results of leukocyte count, NLR, CRP, albumin, protein levels in the blood and micro albumin levels in 24-hour urine.

The oldest mechanism mentioned for kidney damage due to hyperuricemia is the accumulation of uric acid crystals in the renal interstitium and causing obstruction in the tubules. Until now other pathological mechanisms underlying hyperuricemia associated kidney damage has been high lightened in many studies (3).

In a study in the rat an association between high uric acid and cardiovascular disease has been reported. Hyperuricemia causes glomerular hypertrophy in the rat (4). Mazzali et al observed in a rat study, following oxonic acid application an increase in uric acid levels caused kidney damage which was regressed by enalapril, and L-arginine. This study also mentioned that increased juxtaglomerular renin secretion and decreased nitric oxide production cause hypertension (5). Okeahiala et al in a study with 840 patients reported that the UA levels were associated with SBP and DBP (6). Our study detected that serum UA level was associated with both SBP and DBP. However, no significant difference was found between blood pressure values in patients with UA> 7.5mg / dl and UA <7.5mg / dl. Studies have shown that uric acid-lowering treatments have no effect on blood pressure. In a study carried out with hypertensive patients, Kaewput W. et al. found that high UA (> 7.5mg / dl) values were associated with increased CKD stage (7). In the light of these data, even though hypertensive patients do not have a direct effect on blood pressure regulation, it is possible to say that uric acid-lowering therapy prevents CKD progression and indirectly affects blood pressure control.

Also recent studies have shown that vascular changes happen in kidney in the presence of hyperuricemia. Ryu et al in a rat study observed that hyperuricemia resulted decreased expression of e-catherin which has a role in the production of NO (8). As a result of disrupted interactions between renal tubular cells; NO, which increases the renal blood flow, decreased so that renal damage has developed (9). Elevated serum uric acid level was associated with microalbuminuria among non-diabetic and non-hypertensive subjects without a history of cardiovascular disease or renal dysfunction (10). In our study, we detected a positive linear correlation between serum UA and the microalbuminuria ($p<0.01$, $r=0.62$). Our findings are compatible with the literature

In recent years, NLR, in addition to CRP, has been shown to be associated with inflammation and is considered an indicator of inflammation. Especially in the cardiovascular diseases there are studies showing that it may be used as a prognostic factor associated with inflammation (11). In a study with non-diabetic 53 patients and 30 healthy subjects, it was found statistically significant difference between patients and healthy control group considering factors such as uric acid, fibrinogen, CRP and NLR. Our study reported a positive relationship between proteinuria, microalbuminuria, serum uric acid levels and NLR. Spahić et al. observed increased amounts of CRP and NLR in acute coronary syndrome in a study of 116 patients, and both values correlated with serum uric acid level. (12) In our study, the serum uric acid level showed positive linear relationship with CRP and NLR levels, we observed statistically significant difference between two groups according to CRP, NLR and serum UA levels.

In our study, creatinine, 24 hours Urinary Protein Excretion (UAE); 24 hours Urinary Albumin Excretion (UAE) values were higher in patients with UA> 7.5mg / dl than patients with UA <7.5mg / dl. In meta-analyses, uric acid-lowering therapy has been shown to decrease creatinine value and increase eGFR value (13). These results belong to a small number of small studies and larger clinical trials are needed. However, the protective effect of uric acid-lowering treatments on kidney function should not be overlooked.

In our study, we found that body mass index (BMI) was associated with the serum UA level. In the literature, it has been mentioned that the risk of developing metabolic syndrome is four times higher in patients with high serum UA levels. (14). Wang and colleagues evaluated the relationship between the BMI and serum UA levels and identified a positive linear correlation between the BMI and serum UA (15). In our study, patients with increased BMI had higher uric acid values. Our findings are consistent with the literature.

As a conclusion, In our study patients with low eGFR had significantly higher UA levels than those with high eGFR. A positive linear relationship has been detected in our study between uric acid levels and NLR and CRP levels, which have been shown to be associated with inflammation and atherosclerosis in recent years. In light of the knowledge about hyperuricemia and its consequences, it is necessary and useful to focus on treatment strategies to reduce or prevent serum uric acid increase in any situation that causes chronic kidney disease.

Conflicts of Interest Statement: None of the authors had any financal or personel relationhips with other individuals or organizations that might inappropriately influence their work during the submission process.

Research Contribution Rate Statement Summary: The authors declare that, they have contributed equally to the manuscript.

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