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Why Serum Uric Acid is Important for the Development of Atherogenic Vascular Disease?

Aterojenik Vasküler Hastalık Gelişimi İçin Ürik Asit Düzeyi Neden Önemlidir?

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ABSTRACT Objective: The aim of study was to investigate association of hyperuricemia with coronary artery disease (CAD), cerebrovascular disease (CeVD), and various cardiovascular risk factors. **Material and Methods:** A total of 4088 outpatients who admitted to our hospital between 2014-2016, and who had a high serum uric acid level (>6 mg/dl) were screened retrospectively. A total of 225 patients with three serum uric acid levels measured at different times were included. Control group consisted of 215 participants with serum uric acid level ≤6 mg/dl. Associations of serum uric acid level with hypertension [HT], diabetes mellitus [DM], CeVD, CAD, chronic kidney disease [CKD]) and cardiovascular risk factors were investigated. **Results:** Prevalences of type 2 DM, HT, and CKD were higher in patient group. There was a negative association between serum uric acid and HDL-cholesterol. There was a lineer association between serum uric acid and atherogenic index. Hyperuricemia increased the risk of CAD and CeVD. **Conclusion:** Serum uric acid was increased in the presence of CeVDs and CAD independent from coexisting HT or DM. Serum uric acid level should be evaluated as a piece of cardiovascular disease puzzle.

Keywords: Uric acid; cerebrovascular disease; coronary artery disease

ÖZET Amaç: Bu çalışmada hiperürisemi ile koroner arter hastalığı (KAH), serebrovasküler hastalık (SVH) ve kardiyovasküler risk faktörleri arasındaki ilişkinin araştırılması amaçlandı. **Gereç ve Yöntemler:** 2014-2016 yılları arasında hastanemize başvuran ve serum ürik asit düzeyi yüksek (>6 mg/dl) olan 4088 hasta retrospektif olarak tarandı. Bir yıl içerisinde 3 kez serum ürik asit ölçümü olan toplam 225 hasta çalışmaya alındı. Kontrol grubu 2 farklı zamanda serum ürik asit düzeyi ≤6 mg/dl ölçülmüş 215 katılımcıdan oluştu. Serum ürik asit düzeyinin komorbid hastalıklarla (hipertansiyon [HT], diabetes mellitus [DM], SVH, KAH, kronik böbrek hastalığı [KBH]) ilişkisi araştırıldı. **Bulgular:** Hasta grubunda tip 2 DM, HT ve KBH prevalansı daha fazlaydı. Serum ürik asit ve HDL-kolesterol arasında negatif bir ilişki vardı. Serum ürik asit ve aterojenik indeks arasında doğrusal bir ilişki vardı. Hiperürisemide, KAH ve SVH görülme riski artmış bulundu. **Sonuç:** Serum ürik asit düzeyi, HT veya DM'den bağımsız olarak kardiyovasküler hastalık varlığında yüksekti. Serum ürik asit düzeyi, kardiyovasküler hastalık bulmacasının bir parçası olarak değerlendirilebilir.

Anahtar Kelimeler: Ürik asit; koroner arter hastalığı; serebrovasküler hastalık

Cardiovascular risk factors should be well defined and controlled in order to prevent cardiovascular diseases (CVDs) which are the leading causes of mortality and morbidity worldwide. Obesity, dyslipidemia, hypertension (HT), diabetes mellitus (DM), smoking, sedantary living, and atherogenic diet are among the classic cardiovascular risk factors. Apart from these well known cardiovascular risk factors, role of serum uric acid in cardiovascular risk assessment has been debated.[1]

Uric acid is the end product of purin metabolism. Although it has been known as an antioxidant agent in plasma, association of hyperuricemia and diseases with increased oxidative stress such as obesity, HT, metabolic syndrome and coronary arter disease (CAD) were reported.[2-4] The underlying mechanism causing this paradox is not clear. It was hypothesed that increase in serum uric acid level might be a defense mechanism. Another explanation for this paradox may be related to its antioxidant effects in plasma and prooxidant effects in the cell.[2]

Although there have been various studies focusing on the association of uric acid in CVDs, role of serum uric acid in the development of CVDs still needs to be clarified. In this study we aim to investigate association of hyperuricemia with CAD and cerebrovascular disease (CeVD), and the association of serum uric acid with various cardiovascular risk factors.

MATERIAL AND METHODS

The study design was approved by local Human Research Ethics Committee (20/08/2015, 2015/263). A total of 4088 outpatients who admitted to our hospital between January 2014 - January 2016, and who had a high serum uric acid level (>6 mg/dl) were screened. Subjects with malignancies, lymphoproliferative, myeloprolipherative diseases, and infections were excluded. A total of 225 patients who had three serum uric acid levels measured at different times in one year were included. Control group consisted of 215 participitants with serum uric acid level ≤6 mg/dl measured at two different times.

Comorbid diseases of the patients (HT, DM, CeVD, CAD, chronic kidney disease [CKD]) and drugs that they used to take including medications for the treatment for hyperuricemia were recorded. Arterial HT was defined as blood pressure ≥140/90 mmHg (mean of two different measurements) or ongoing pharmacologic treatment.[5] Diabetes mellitus was defined as fasting plasma glucose ≥126 mg/dL or plasma glucose ≥200 mg/dL 2 hours after a 75-g oral glucose load or ongoing pharmacologic treatment.[6] Diabetic people with HbA1c level <7% were accepted as 'well controlled', where as HbA1c level >7% was accepted as "not well controlled". Chronic kidney disease was defined as kidney damage (such as albuminuria, urine sediment abnormalities, tubular disorders, abnormalities detected by histology, structural abnormalities detected by imaging or history of kidney transplantation) or estimated glomerular filtration rate (eGFR) below 60 mL/min per 1.73m^2, for 3 months or further.[7] Coronary artery disease was defined as history of myocardial infarction or percutaneous transluminal coronary angioplasty or coronary artery bypass graft. Cerebrovascular disease was defined as previous stroke attributed to ischemic or hemorrhagic lesions in the brain.[8]

Demographic, clinical, and biochemical features of participants were investigated retrospectively. Serum creatinine, urea, uric acid, fasting blood glucose, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), aspartate aminotransferase, alanine aminotransferase, albumin, alkaline phosphatase, gamma glutamyl transpeptidase, biluribin, sodium, potassium, calcium, phosphorus, albumin, high sensitve C reactive protein (hCRP), glycosylated hemoglobin (HbA1c) were obtained by Roche Cobas C501 Chemistry Immunoanalyzer Low-density lipoprotein cholesterol (LDL-C) was calculated by Friedewald formula: LDL-C= (TC)- (HDL-C) - (TG/5).[9] Atherogenic index was calculated as log [TG/HDL-C].[10] Urine analysis was performed by Iris IQ 200 automa ted urine analyser. Twenty-four-hour urine protein (mg/day) was assessed with Cobas Integra 800 Chemistry Analyzer. Estimated glomerular filtration rate was calculated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula: $141 \times \min(Scr/\kappa,1)^{\alpha} \times \max(Scr/\kappa,1)^{-1.209} \times 0.993^{age} \times 1.018$ [female] $\times$ 1.159 [black].[7]

Association of serum uric acid with comorbid diseases of the subjects (HT, DM, CeVD, CAD, CKD), and cardiovascular risk factors was investigated.

STATISTICAL ANALYSIS

For continuous variables, Student's *t* Test was used for the comparison of mean values of 2 groups, and one way variance analysis (ANOVA) was used to compare averages of more than 2 groups. Descriptive statistics were shown as mean±standard deviation. Chi-squared test is used for categoric data. Numbers and percentage values were given for categorical variables as descriptive statistics. Logistic regression analysis was performed to find out the independent risk factors, and Exp(B) values were given with confidence interval. *p* value <0.05 was accepted as statistically significant.

RESULTS

Group 1 consisted of 225 patients (103 female, 122 male) with serum uric acid >6 mg/dl, whereas group 2 consisted of 215 participitants (133 female, 82 male) with serum uric acid level ≤6 mg/dl. Serum uric acid level of patients were significantly higher than the control group (p <0.001). Patient group had higher hCRP values (p=0.001). Mean atherogenic index was lower in control group, whereas mean HDL-C value of control group was higher (p<0.001). Prevalence of type 2 DM, HT, and CKD were higher in patient group (p < 0.001). There was not significant difference between HbA1c levels of diabetic patients in patient and control groups (p=0.461). Serum uric acid levels of diabetic people who were well controlled (HbA1c <7%) and not well controlled (HbA1c > 7%) were not significantly different (p=0.757). Use of thiazides was more common in the patient group (p = 0.002). Baseline characteristics and laboratory data of patient and control groups were summarized in Table 1.

When all participients in two groups were evaluated, males were found to have higher serum uric acid level than females (7.1±2.6 vs 6.1±3.2 mg/dl) (p <0.001). There was no significant association between *menopause status* and uric acid level in females of two groups (p=0.079). Participitants who used thiazide diuretics (n=32) had higher serum uric acid level (8.5±2.5 mg/dl) than the ones (n=371) who did not (6.6±3.1 mg/dl) (p=0.001). Serum uric acid levels of patients with and without type 2 DM, CKD, CeVD, CAD are shown in (Table 2).

TABLE 1: Demographic and laboratory features of patient and control groups.

	Patient Group (n: 225)	Control Group (n: 105)	p value
Age (years)	61.31±7.69	44.40±10.27	< 0.001
Female / Male (n/n)	103 / 122	133 / 82	0.
Hypertension (n)	168	52	< 0.001
Diabetes mellitus (n)	100	48	< 0.001
Chronic kidney disease (n)	135	23	< 0.001
Use of thiazide diuretics (n)	26	6	0.002
Serum uric acid (mg/dl)	8.6 ± 2.7	4.47 ± 1.3	< 0.001
hCRP (mg/l)	132	19	0.001
Total cholesterol (mg/dl)	195	209	0.088
LDL-C (mg/dl)	120	123	0.718
HDL-C (mg/dl)	39	52	< 0.001
Triglycerides (mg/dl)	178	158	0.153
Atherogenic index	0.64	0.44	< 0.001
HbA1c (%)	7.1±.35	6.8±1.26	0.471

Abbreviations: hCRP: high sensitive C reactive protein; **LDL-C:** low density lipoprotein cholesterol; **HDL-C:** high density lipoprotein cholesterol.

In two groups, a lineer positive association was present between serum uric acid and age (r=0.494; p <0.001), whereas a moderate, negative, lineer association was present between serum uric acid and eGFR (r=-0.534; p <0.001). Uric acid level was similar in participitants with CKD who required renal replacement treatment (n=25) and who did not (n = 97) (p=0.998). There was a negative association between serum uric acid and HDL-C (r=-0.337; $p \leq$ 0.001). However, serum uric acid was not found associated with TG, and LDL level (p>0.05). There was a lineer association between serum uric acid and atherogenic index (r =0.303; p < 0.001).

Coronary artery disease and CeVD were more prevalent in the patient group (p<0.001) (Figure 1). Risk of HT and DM in patients with hyperuricemia was increased (OR: 8.615, 95% CI: 5.575-13.313, OR: 2.783, 95% CI: 1.838-4.215, respectively) (p < 0.001). Risk of CeVDs and CAD in patients with hyperuricemia was also found higher than the control group (OR:8.19, 95% CI: 3.407-19.688, OR: 12.301, CI: 6.489 - 23.320, respectively) (p < 0.001) (Table 3).

TABLE 2: Mean serum uric acid levels of subjects according to gender, use of thiazide diuretics and presence of comorbidities.

			Serum uric acid	
		n	(mg/dl)	p value
Gender	Male	204	7.1±2.6	< 0.001
	Female	234	6.1±3.2	
Thiazide diuretics	+	32	8.5±2.5	0.001
	-	371	6.6±3.05	
Hypertension	+	220	7.78±3.00	<0.001
	-	207	5.50±2.57	
Type 2 DM	+	147	7.5±3.0	< 0.001
	-	291	6.1±2.9	
CKD	+	158	8.3±2.5	< 0.001
	-	280	5.7±2.8	
CeVD	+	49	8.2±2.3	< 0.001
	-	388	6.4±3.03	
CAD	+	107	8.9±3.6	< 0.001
	-	330	5.8±2.4	

Abbreviations: hCRP: high sensitive C reactive protein; **LDL-C:** low density lipoprotein cholesterol; **HDL-C:** high density lipoprotein cholesterol.

DISCUSSION

Role of serum uric acid in the development of cardiovascular diseases has been debated.[1,3] Increased prevalence of hyperuricemia was reported in disorders like HT, DM, dyslipidemia, and obesity. All of these comorbidites may contribute to the development of CVDs including CAD and CeVD independent from serum uric acid level.[3,11,12] Thus, association of hyperuricemia and CVDs may be confounded by these disorders.[3] However, elevation of serum uric acid prior to the development of HT or metabolic syndrome was reported in the literature.[13] Our study results revealed the increased prevalence of CVDs in patients with hyperuricemia as well as increased prevalences of HT, type 2 DM, and CKD. Hyperuricemia was found to increase the independent risk of CAD 12.3 times and CeVD 8.19 times in our study.

Evidence suggested that the effect of uric acid on CVD occur mainly at the vascular level.[14] Increased serum uric acid was reported as an independent risk factor for endothelial dysfunction.[15] Hyperuricemia may also lead to the development of HT. The underlying mechanisms include reduction of endothelial nitric oxide levels, stimulation of oxidative stress, activation of the renin–angiotensin system, proliferation of vascular smooth muscle cells, and the development of microvascular disease in the kidney.[13] Besides, hyperuricemia may activate epithelial sodium channels, which may also contribute to the development of HT.[4] Risk of HT in patients with hyperuricemia was found 6.615 times higher in our study.

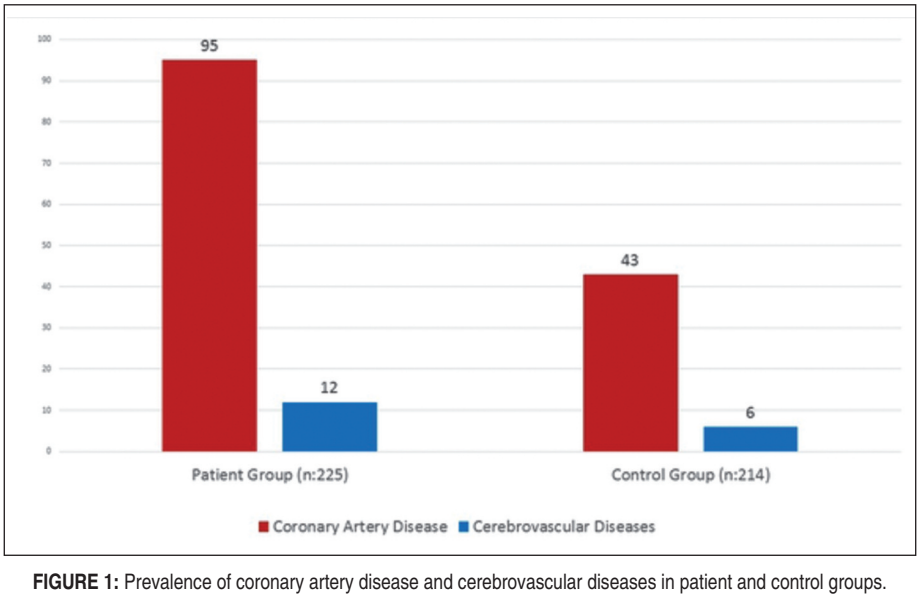

FIGURE 1: Prevalence of coronary artery disease and cerebrovascular diseases in patient and control groups.

TABLE 3: Risk of hypertension, type 2 diabetes mellitus, cerebrovascular diseases and coronary artery disease in patients with hyperuricemia.

	OR	95% CI for OR	p value
HT	8.615	5.575-13.313	< 0.001
Type 2 DM	2.783	1.838-4.215	< 0.001
CeVD	8.190	3.407-19.688	< 0.001
CAD	12.301	6.489-23.320	< 0.001

Abbreviations: HT: hypertension, **DM;** diabetes mellitus, **CeVD;** Cerebrovascular diseases, **CAD;** coronary artery disease, **OR;** Odds ratio, CI; confidence interval.

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Hyperuricemia may cause increased oxidative stres.[16] Xanthine oxidase which involves in purine catabolism and production of uric acid from hypoxanthine is known as one of the main sources of oxidative stress within the endothelial cells that contribute to the development of inflammation and endothelial dysfunction.[14,17] Reduction in availability of endothelial nitric oxide and vascular activation of the renin–angiotensin system take part in the process.[14,17] Higher hCRP values may indicate increased oxidative stress in patients with hyperuricemia in our study. Oxidative stress due to increased serum uric acid may affect multiple cells including pancreatic β cells and involved in insulin resistance.[18] Serum uric acid level of patients with type 2 DM was also found higher in our study and the risk of having DM was increased 2.7 times higher in hyperuricemia. Serum uric acid levels of diabetic people who were well controlled and not well controlled were not significantly different in our study.

Previous reports indicated the association between hyperuricemia and high TG level and low HDL-C.[12] Positive correlation was reported between serum uric acid and atherogenic index which was one of the parameters used in CVD risk analysis.[4,19] Our results supported the negative association between serum uric acid and HDL-C, and positive correlation between serum uric acid and atherogenic index. Positive correlation between serum uric acid and atherogenic index might be due to decreased HDL-C.[11] This may also contribute to the role of hyperuricemia in the development of cardiovascular diseases.

We found that hyperuricemia increased the risk of CeVD 8.19 times. Association of hyperuricemia and hemorrhagic or ischemic stroke was reported in various studies.[20-22] However, there are some reports indicating that hyperuricemia alone does not appear to confer an increased risk of stroke, whereas its association with stroke related risk factors such as HT, and DM was reported.[23]

The limitation of this study is mostly attributed to its retrospective design. Serum uric acid is affected from many factors such as diet, body mass index, smoking history, alcohol use, physical inactivity which were not considered in our study, and these factors might affected our study results.[24] Effect of the drugs on the outcome could not be evaluated as the number of the subgroups was limited. Another limitation was that CVD diagnosis only depended on the history of the patients and this might lead underdiagnosis of patients.

In conclusion patients with HT, DM, CKD, CAH, and CeVD had higher serum uric acid level. Serum uric acid was increased in the presence of CVDs independent from coexisting HT or DM. Therefore, serum uric acid level should be evaluated as a piece of CVD puzzle and clinicians should interpret serum uric acid level in this point of view.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Serap Demir, Simge Bardak, Kenan Turgutalp;* ***Design:*** *Kenan Turgutalp, Asena Ayça Özdemir, Mustafa Kemal Mavi;* ***Control/Supervision:*** *Serap Demir, Ahmet Kıykım;* ***Data Collection and/or Processing:*** *Utku Uluköksal, Mustafa Kemal Mavi, Mahmut Görkem Gürçınar, Mahmut Bakır Koyuncu;* ***Analysis and/or Interpretation:*** *Simge Bardak, Asena Ayça Özdemir, Mahmut Bakır Koyuncu;* ***Literature Review:*** *Mahmut Bakır Koyuncu, Mürşide Esra Dolarslan, Utku Uluköksal;* ***Writing an Article:*** *Simge Bardak; Mürşide Esra Dolarslan;* ***Critical Review:*** *Serap Demir, Ahmet Kıykım, Kenan Turgutalp.*

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