Ankara Med J, 2018;(3):369-74
DOI: 10.17098/amj.461376

Is There a Prognostic Significance of Serum Uric Acid Level in Cardiac Dysfunction?

Serum Ürik Asit Düzeyinin Kardiyak Disfonksiyonda Prognostik bir Önemi Var mıdır?

Canan Topçuoglu[1], Sevilay Sezer[1], Çiğdem Yücel[1], Mustafa Çetin[2], Fatih Dede[3], Turan Turhan[1]

[1]Ankara Numune Training and Research Hospital, Medical Biochemistry Clinic
[2]Ankara Numune Training and Research Hospital, Cardiology Clinic
[3]Ankara Numune Training and Research Hospital, Nephrology Clinic

Abstract
Objectives: Uric acid (UA) is the end-product of purine metabolism and is a well-known risk factor for gout disease. In addition to that, elevated serum UA levels have been associated with many disorders including insulin resistance, obesity, hypertension, renal dysfunction and hypothyroidism. On the other hand, whether uric acid has any causal relationship with cardiovascular morbidity is a debated issue.
Materials and Methods: This retrospective study included totally 326 patients who were inpatients at the Cardiology Ward or Coronary Intensive Care Unit of Ankara Numune Training and Research Hospital between March 2016 and February 2017. Data regarding serum UA and N-terminal pro B-type Natriuretic Peptide (NT-proBNP) levels and left ventricular ejection fraction %) LVEF) were retrieved from the hospital information system. Patients were categorized into four groups based on their UA levels (Group 1 UA: 2.7-4.9 mg/dL, Group 2 UA: 5-6 mg/dL, Group 3 UA: 6.1-7.4 mg/dL, Group 4 UA: 7.5-15.6 mg/dL). Other parameters were compared between the groups using ANOVA test. Additionally, the effects of gender, age and eGFR were also examined when evaluating the changes in left ventricular function according to UA levels. Correlation between the variables was analyzed with Pearson's correlation test.
Results: Group 4 was significantly different than the rest of the groups in terms of age, NT-proBNP and eGFR ($p<0.001$). In addition, group 4 showed significant difference from Group 1 and Group 3 regarding %LVEF ($p=0.006$ and $p=0.002$, respectively). However, the differences between the groups regarding %LVEF was not influenced by age or eGFR. Regardless of the groups, serum UA levels showed statistically significant but weak positive correlation with NT-proBNP ($r=0.310$, $p<0.001$), and low level of negative correlation with % LVEF, which was statistically significant ($r=-0.173$, $p=0.002$).
Conclusion: Based on our findings, we concluded that serum UA level has prognostic significance in cardiac dysfunction and can be used in the follow-up of such patients.
Key words: Cardiac dysfunction, NT-proBNP, uric acid.

Öz
Amaç: Ürik asit, pürin metabolizmasının son ürünü ve gut için iyi bilinen bir risk faktörüdür. Bununla birlikte, yüksek serum ürik asit düzeyleri insülin rezistansı, obezite, hipertansiyon, renal disfonksiyon, hipotiroidi gibi birçok hastalıkla ilişkili bulunmuştur. Öte yandan, ürik asidin kardiyovasküler morbiditede nedensel bir rol oynayıp oynamadığı tartışılmaktadır. Çalışmamızda serum ürik asit (ÜA) ve kalp yetmezliği prognostik belirteci olan N terminal pro B-tipi Natriüretik Peptit (NT-proBNP) düzeyleri ile sol ventrikül fonksiyon bozukluğu arasında ilişki olup olmadığını araştırmayı amaçladık.
Materyal ve Metot: Çalışma retrospektif olarak planlandı. Mart 2016 ile Şubat 2017 tarihleri arasında Ankara Numune Eğitim ve Araştırma Hastanesi Kardiyoloji Servisi ve Koroner Yoğun Bakımda yatan 326 hasta çalışmaya dahil edildi. Bu hastaların serum ÜA, NT-proBNP düzeyleri ile ejeksiyon fraksiyonu (EF) bulguları hastane enformasyon sisteminden alındı. Hastalar serum ÜA düzeylerine göre 4 gruba ayrıldı (1. grup ÜA; 2,7-4,9 mg/dL, 2. grup ÜA; 5-6 mg/dL, 3. grup ÜA; 6,1-7,4 mg/dL, 4. grup ÜA; 7,5-15,6 mg/dL). Gruplar arasında parametreler ANOVA testi kullanılarak karşılaştırıldı. Ayrıca, sol ventrikül disfonksiyon bulgularında ürat düzeylerine göre değişimler incelenirken, cinsiyet, yaş ve eGFR 'nin bu parametreler üzerindeki etkileri değerlendirildi. Değişkenler arasında ilişki için Pearson korelasyon testi kullanıldı.
Bulgular: 4. grup; yaş, NT-proBNP, eGFR diğer gruplardan anlamlı düzeyde farklıydı ($p<0.001$). EF, 4. grup ile 1. ve 3. gruplar arasında anlamlı farklı bulundu (sırası ile p=0,006 and p=0,002). Ancak EF'nun

gruplar arasındaki farklılıkları üzerinde yaş ve eGFR etkisinin olmadığı görüldü. Gruplardan bağımsız olarak serum ÜA düzeyi ile NT-proBNP arasında istatistiksel olarak anlamlı ancak zayıf pozitif korelasyon (r=0,310, p<0,001), % LVEF arasında ise düşük düzeyde ancak anlamlı negatif korelasyon (r=-0,173, p=0,002) tespit edildi.
Sonuç: Çalışmamızdaki bulgulara göre serum ÜA düzeyinin kardiyak disfonksiyonda prognostik öneme sahip olduğu ve hastaların takibinde kullanılabileceği kanısına varılmıştır.
Anahtar kelimeler: Kardiyak disfonksiyon, NT-proBNP, ürik asit.

Correspondence / Yazışma Adresi:
Dr. Canan Topçuoğlu
Ankara Numune Training and Research Hospital, 06100, Ankara / Turkey
e-mail: cananyy@yahoo.com
Date of submission: 06.12.2017
Date of admission: 10.08.2018

Introduction

Uric acid (UA), which is a weak acid, is mainly produced in liver, intestinal system, muscle, kidney and vascular endothelial cells through a reaction catalyzed by xanthine oxidase (XO) as an end-product of purine metabolism. It is mainly excreted through kidneys.[1] Primary or secondary hyperuricemia is caused by reduced UA excretion through kidneys in 85-90% of the cases. On the other hand, elevated UA levels can also be caused by a purine-rich diet, alcohol consumption and conditions associated with high cellular turnover such as tumoral lysis and psoriasis.[2]

UA is a potent scavenger of peroxynitrite and reactive oxygen radicals and is an anti-oxidant molecule.[3] It can have a key role in tissue healing process by inducing endothelial cell mobilization and the inflammatory process that is required for tissue repair.[4] More than half of the plasma anti-oxidant capacity is provided by UA. Due to its antioxidant property, UA has been shown to be protective against neurological diseases such as Multiple Sclerosis, Parkinson's and Alzheimer's diseases.[1]

In addition to its roles in pathogenesis of gout and kidney stones, UA has long been known to be associated with various diseases including hypertension (HT), Cardiovascular Diseases (CVD), Metabolic Syndrome (MS), insulin resistance and Diabetes Mellitus (DM).[5] The prevalence of MS has been reported to be 10 times higher among individuals with normal body mass index in the presence of serum UA levels greater than 10 mg/dL when compared to those with UA levels lower than 6 mg/dL.[6] Studies have shown that elevated serum UA levels are associated with DM and insulin resistance.[7,8] There is in increased hepatic glucose production in the presence of insulin resistance and type 2 DM. Intracellular UA induces the enzyme Adenosine Monophosphate Dehydrogenase (AMPD), a stimulator of hepatic gluconeogenesis, while inhibiting the enzyme Adenosine Monophosphate Protein Kinase (AMPK), an inhibitor of hepatic gluconeogenesis.[9] Reduction of nitric oxide (NO) caused by hyperuricemia also contribute to development of insulin resistance.[10]. It has been shown that high UA levels are associated with HT, even within the reference interval.[11] By causing smooth muscle cell proliferation and production of low grade inflammatory and vasoconstrictor substances, elevated UA levels lead to growth, instability and rupture of atherosclerotic plaques, facilitate thrombus formation, and thus, precipitate microvascular diseases.[2]

Besides studies that show UA as an independent risk factor for CVD, presence of other studies with contradicting findings has resulted in a controversy about the relationship between hyperuricemia and CVD.

Therefore, in the present study, we aimed to investigate whether serum UA levels are associated with N-terminal pro B-type Natriuretic Peptide (NT-proBNP), a prognostic marker for heart failure, and with left ventricular dysfunction.

Materials and Methods

The study was designed as a retrospective study. Totally 326 patients who were admitted to Cardiology Clinic or Coronary Intensive Care Unit of Ankara Numune Training and Research Hospital between March 2016 and February 2017 were included in the study. Data regarding concurrently measured serum UA and NT-proBNP levels (Reference intervals are <75 years; 0-300 ng/L and ≥75 years; 0-450 ng/L) and left ventricular ejection fraction (% LVEF) from echocardiographic assessment on the same day were retrieved from the hospital information system. Serum UA levels were measured with Beckman Coulter AU 5800 (Beckman Coulter, USA) analyzer. Plasma NT-proBNP levels were measured with fluorescence immunoassay using Finecare FIA meter (Katalogno.W202, Gguanghou, P.R. China). Measuring range and lower limit of detection for NT-proBNP measurement were 18-35.000 ng/dL, and 18 ng/dL, respectively. Estimated glomerular filtration rate (eGFR) was calculated with MDRD formula and patients were divided into two groups with eGFR levels ≥65 and <65.

Patients were categorized into 4 groups based on serum UA levels according to Yamauchi et al, ; Group 1 UA level: 2.7-4.9 mg/dL, Group 2 UA level: 5-6 mg/dL, Group 3 UA level: 6.1-7.4 mg/dL and Group 4 UA level: 7.5-15.6 mg/dL [12]. The groups were compared in terms of age, NT-proBNP, non-HDL cholesterol, white blood cell (WBC) count, eGFR and % LVEF.

Statistical Analysis

Study parameters were compared across the groups using ANOVA test. In addition, when evaluating the changes in left ventricular dysfunction findings according to UA levels, the effects of gender, age and eGFR on these parameters were evaluated with logistic regression analysis. Correlation between the variables was analyzed with Pearson's correlation test.

Results

Serum UA levels and distribution of age, NT-proBNP and % LVEF values in groups created according to UA levels are presented in Table 1.

Accordingly, in Group 4, mean patient age and plasma NT-proBNP levels were significantly higher in comparison to the rest of the groups ($p < 0.001$). In Group 4, % LVEF was significantly different compared to Group 1 and Group 3 ($p=0.006$ and $p=0.002$, respectively). However, age and eGFR were found to have no effect on the differences between the groups regarding % LVEF. The correlations of serum UA level with NT-proBNP and % LVEF were analyzed independent of the groups, and accordingly, there was a weak positive correlation between UA and NT-proBNP, which was statistically highly significant ($r=0.310$, $p<0.001$) and a low level of negative correlation between UA and % LVEF, which was statistically significant ($r=-0.173$, $p=0.002$) (Table 2). When the controlled variable was age, there were weak but

significant correlation between serum UA and NT-proBNP levels and % LVEF (r=0.248, p<0.001 and r=-0.142, p=0.009, respectively). There were weak but statistically significant correlation between serum UA level and serum NT-proBNP levels and % LVEF, which was a sex-controlled variable (r=0.312, p<0.001 and r=-0.178, p=0.001, respectively).

Table 1. Groups and parameters according to UA levels.

		Group 1 (n=83)	**Group 2 (n=81)**	**Group 3 (n= 85)**	**Group 4 (n= 77)**	**p**
UA mg/dL		2.7-4.9	5-6	6.1-7.4	7.5-15.6	
Male, n (%)		52 (62.66)	63 (77.78)	64 (75.29)	45 (58.44)	
Age, mean±SD		59.42±14.33	62.43±12.85	61.35±14.61	69.47±14.26	<0.001
NT-proBNP ng/L, median (IQR)		464 (1381)	517 (1401)	398 (1441)	3086 (6691)	<0.001
% LVEF, mean±SD		50.99±11.80	48.31±13.87	51.78±12.33	43.61±16.77	0.006[a] 0.002[b]
eGFR, n (%)	≥65	80 (96.39)	69 (85.19)	58 (68.23)	32 (41.56)	
	<65	3 (3.61)	12 (14.81)	27 (31.77)	45 (58.44)	

[a]Between Group 4 and Group 1, [b]Between Group 4 and Group 3.

Discussion

Our study results showed that Group 4, which had the highest UA level, had higher NT-proBNP levels and lower % LVEF compared to the other groups. In their study, Yamauchi et al. examined the association between serum UA, BNP, % LVEF and left ventricular mass index (LVMI), and similar to our results, they showed that as UA level increased, BNP level and LVMI increased, and % LVEF decreased.[12] In another study including patients with heart failure, a highly strong inverse relationship was found between serum UA level and % LVEF.[13, 14]

Table 2. Correlation serum UA level between age, NT-proBNP and %LVEF.

	Serum UA	
	r	p
Age	0.272	<0.001
NT-ProBNP	0.310	<0.001
% LVEF	-0.173	0.002

Serum UA level also reflects XO enzyme activity. Increased XO enzyme activity in patients with heart failure suggests that it may play an important role in pathophysiological events of heart failure such as oxidative stress, apoptosis in myocytes, and cardiac mechano-electric dissociation.[15]

The association between serum UA levels and CVD may involve risk factors often encountered in cardiac disease or may be independent of these factors as well. These risk factors include DM, dyslipidemia, HT, alcohol consumption, hypothyroidism and diuretic use. Independent of the risk factors, increased serum UA levels albeit in normal reference range has been shown to cause impairment in flow-mediated dilation in brachial arteries, increased carotid media intima thickness and aortic atherosclerosis in healthy individuals [3]. A rat study showed that UA stimulated phosphorylation of platelet derived growth factor receptor β (PDGFRβ).[16] This may explain increased vascular smooth muscle cell proliferation and higher prevalence of CVD's observed in hyperuricemic patients.[3] Elevated UA levels cause increased activity of NADPH oxidase, and in turn, increased production of reactive oxygen species (ROS). Increased ROS leads to vascular injury through various mechanisms involving reduced ATP, increased phosphorylation of PDGFRβ, induction of renin angiotensin system, mitochondrial injury and increased apoptosis.[3] Increased oxidative stress in hyperuricemia may lead to reduced NO synthesis and thus, disturbance in peripheral vasodilation capacity.[3] Studies that investigated whether serum UA is an independent risk factor for CVD had contradicting results. Framingham heart study could not find association between UA and coronary heart disease (CHD) or cardiovascular mortality.[17] Later studies have shown serum UA as an independent predictor of CHD, and found a positive correlation between serum UA level and the severity of CHD.[18, 19] One study including middle-aged patients with 7- 17 years follow-up time showed higher risk of myocardial infarction, heart failure and stroke in patients with high basal serum UA levels.[20]

One study that compared serum UA levels and the severity of heart failure, which was assessed with New York Heart Association *(*NYHA) score, found higher serum UA levels among patients in NYHA groups III and IV.[21]

Unlike our results, Zeng et al. did not find difference regarding % LVEF between subsets of patients according to serum UA. In their study including type 2 diabetic kidney patients, they categorized patients into 4 groups based on their serum UA levels. The researchers reported that there was no difference between the groups regarding % LVEF (p=0.352), whereas LVMI and frequency of left ventricular hypertrophy (LVH) were different between the groups.[22]

In our study, we found that serum UA level showed positive correlation with NT-proBNP and negative correlation with % LVEF, independent of the groups. While one study also showed positive correlation between UA and BNP, there were studies showing negative correlation between UA and % LVEF, or others that did not find any correlation as well.[14,22]

Based on our findings, it is concluded that serum UA level has prognostic significance in cardiac dysfunction as NT-proBNP, and that it can be used in follow-up of such patients.

Limitations

Limitations of the present study include lack of evaluation of LVMI, which is LVH's indicator and have importance in assessment of cardiac function.

Authors declare that they have no conflict of interest. No financial support was received.

References

1. El Ridi R, Tallima H. Physiological functions and pathogenic potential of uric acid: A review. J Adv Res 2017;8:487-93.
2. Martínez-Quintana E, Tugores A, Rodríguez-González F. Serum uric acid levels and cardiovascular disease: the Gordian knot. J Thorac Dis 2016;8(11):E1462-E1466.
3. Ames BN, Cathcart R, Schwiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. Proc Natl Acad Sci USA 1981;78(11):6858–62.
4. Nery RA, Kahlow BS, Skare TL, Tabushi FI, do Amaral e Castro A. Uric acid and tissue repair. Arq Bras Cir Dig 2015;28(4):290–2.
5. Sharaf El Din UAA, Salem MM, Abdulazim DO. Uric acid in pathogenesis of metabolic, renal and cardiovascular diseases. A review. J Adv Res 2017;8:537-48.
6. Choi HK, Ford ES. Prevalence of the metabolic syndrome in individuals with hyperuricemia. Am J Med 2007;120(5):442–7.
7. Krishnan E, Pandya BJ, Chung L, Hariri A, Dabbous O. Hyperuricemia in young adults and risk of insulin resistance, prediabetes, and diabetes: a 15-year follow-up study. Am J Epidemiol. 2012;176(2):108–16.
8. Shani M, Vinker S, Dinour D, et al. High normal uric acid levels are associated with an increased risk of diabetes in lean, normoglycemic healthy women. J Clin Endocrinol Metab 2016;101(10):3772–8.
9. Cicerchi C, Li N, Kratzer J, Garcia G, et al. Uric acid-dependent inhibition of AMP kinase induces hepatic glucose production in diabetes and starvation: evolutionary implications of the uricase loss in hominids..FASEB J 2014;8:3339–50.
10. Roy D, Perreault M, Marette A. Insulin stimulation of glucose uptake in skeletal muscles and adipose tissues in vivo is NO dependent. Am J Physiol 1998;274(4 Pt 1):E692-9.
11. Leiba A, Vinker S, Dinour D, Holtzman EJ, Shani M. Uric acid levels within the normal range predict increased risk of hypertension: a cohort study. J Am Soc Hypertens 2015;9(8):600–9.
12. Yamauchi Y, Fujita Shu, Shibata K, et al. Is Serum Uric Acid Independently Associated With Left Ventricular Mass Index, Ejection Fraction, and B-Type Natriuretic Peptide Among Female and Male Cardiac Patients? Int Heart Jm. 2017;58(4):562-9.
13. Borghi C, Cosentino ER, Rinaldi ER, Cicero AF. Uricaemia and ejection fraction in elderly heart failure outpatients. Eur J Clin Invest 2014;44(6):573-8.
14. Amin A, Vakilian F, Maleki M. Serum uric acid levels correlate with filling pressures in systolic heart failure. Congest Heart Fail 2011;17:80–4.
15. Duan X, Ling F. Is uric acid itself a player or a bystander in the pathophysiology of chronic heart failure? Med Hypotheses 2008;70 (3):578–81.
16. Kırça M, Oğuz N, Çetin A, Uzuner F, Yeşilkaya A. Uric acid stimulates proliferative pathways in vascular smooth muscle cells through the activation of p38 MAPK, p44/42 MAPK and PDGFRb. J Recept Signal Transduct Res 2017;37(2):167-73.
17. Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. Ann Intern Med 1999;131(1):7–13.
18. Jayashankar CA, Andrews HP, Vijayasarathi Pinnelli VB, et al. Serum uric acid and low-density lipoprotein cholesterol levels are independent predictors of coronary artery disease in Asian Indian patients with type 2 diabetes mellitus. J Nat Sci Biol Med 2016;7(2):161–5.
19. Ekici B, Kütük U, Alhan A, Töre HF. The relationship between serum uric acid levels and angiographic severity of coronary heart disease. Kardiol Pol 2015;73(7):533–8.
20. Holme I, Aastveit AH, Hammar N, Jungner I, Walldius G. Uric acid and risk of myocardial infarction, stroke and congestive heart failure in 417,734 men and women in the Apolipoprotein MOrtality RISk study (AMORIS). J Intern Med 2009;266(6):558–70.
21. Khan A, Shah MH, Khan S, Shamim U, Arshad S. Serum Uric Acid level in the severity of Congestive Heart Failure (CHF). Pak J Med Sci 2017;33(2):330-4.
22. Zeng C, Cheng D, Sheng X, et al. Increased Serum Uric Acid Level Is a Risk Factor for Left Ventricular Hypertrophy but Not Independent of eGFR inbPatients with Type 2 Diabetic Kidney Disease. J Diabetes Res 2017 (doi: 10.1155/2017/5016093).