Shiraz E-Med J. 2016 February; 17(2):e35007. doi: 10.17795/semj35007.

Published online 2016 February 28. **Research Article**

Comparison of Serum Uric Acid Concentrations in Subjects With and Without Atrial Fibrillation

Mohammad Aghaali,[1,*] Seyed Fakhreddin Hejazi,[2] Leili Iranirad,[2] and Akram Heidari[3]

[1]General Practitioner, Qom University of Medical Sciences, Qom, IR Iran
[2]Department of Cardiology, Qom University of Medical Sciences, Qom, IR Iran
[3]Department of Community Medicine, Qom University of Medical Sciences, Qom, IR Iran

[*]*Corresponding author*: Mohammad Aghaali, General Practitioner, Qom University of Medical Sciences, Saheli Street, Qom, IR Iran. Tel: +98-9127515639, Fax: +98-2532853377, E-mail: dr.aghaali@yahoo.com

Received 2015 December 11; **Revised** 2016 January 15; **Accepted** 2016 February 14.

Abstract

Background: Uric acid, a product of purine degradation, is a risk factor for cardiovascular disease. Studies have demonstrated a relationship between uric acid and increased inflammatory and oxidative stress in the general population. Recent studies also confirmed the role of inflammatory factors and oxidative stress in atrial fibrillation (AF).
Objectives: The purpose of this study was to investigate the relationship between serum uric acid levels and the risk of AF.
Patients and Methods: This case-control study consisted of 32 patients with AF and 32 healthy controls. Both groups were matched by age, sex, and underlying disease. The diagnosis of AF was based on an electrocardiogram and confirmed by a cardiologist. Patients with heart failure, coronary artery disease, recent infection, renal failure, thyroid disorders and malignancy or who were treated with drugs affecting serum uric acid were excluded. The uric acid levels in both groups were measured using an enzymatic method. The mean serum uric acid of the two groups was compared with a t-test and SPSS software.
Results: The female to male ratio in the two groups was 1.28. The mean age of the patients in the AF group and control group was 69.12 $\pm$ 11.8 and 67.75 $\pm$ 14.8, respectively. There were no significant differences in the age and sex of the two groups. The mean serum uric acid in the AF group and control group was significantly different (5.79 $\pm$ 1.19 mg/dL and 4.81 $\pm$ 1.26 mg/dL, respectively; P = 0.002).
Conclusions: The results suggest that serum uric acid can be considered a risk factor for AF. Further studies are recommended to investigate the role of uric acid reduction in the prevention and treatment of AF.

Keywords: Atrial Fibrillation, Adult, Uric Acid

1. Background

Uric acid is produced via the action of the xanthine oxidase enzyme and is the end product of purine degradation in humans (1). In both men and women, the level of serum uric acid increases with age. In premenopausal women, the levels of serum uric acid are lower than those of men because of the uricosuric effect of estrogen, whereas they increase significantly after menopause (2).

In most mammals, plasma uric acid levels are reduced by urate conversion into allantoin in the liver. However, in humans, the uricase gene is nonfunctional (3), resulting in higher and more fluctuating serum uric acid levels in humans than in other mammals (4). Ames proposed that due to the uric acid antioxidant, properties mutation of the uricase gene gave humans an evolutionary advantage over other primates (5). However, the actual importance of uric acid in humans remains uncertain. Research has demonstrated that an infusion of uric acid reduced oxidative stress (6), but it is not known whether lower levels of uric acid are associated with accelerated aging. Although the uric acid levels of women are about 20% lower than those of men, on average, women live about 7.5 years longer than men (7).

In the general population, uric acid was shown to be a risk factor for poor health outcomes (8). Serum uric acid levels, independently of other risk factors, were reported to be associated with cardiovascular events (9). The same study showed that 29% of the benefit, in terms of cardiovascular risk, associated with losartan compared with atenolol treatment was attributable to a decrease in serum uric acid.

Atrial fibrillation (AF) is the commonest sustained arrhythmia, and its prevalence increases in accordance with age. It can cause heart failure, thromboembolism, and stroke, and it is associated with increased mortality and morbidity (10). The Framingham Heart study, a population-based prospective study, showed that the risk of AF increased with advancing age. In addition, patients with congestive heart failure, valvular heart disease, my-

ocardial infarction, diabetes and hypertension had a significantly higher risk of developing AF (10).

The exact mechanisms of the initiation and maintenance of AF are uncertain. However, research has shown that oxidative stress and inflammation play a role in the initiation and maintenance of this disease, as evidenced by interstitial fibrosis and infiltration of inflammatory cells in atrial tissue (11). Another study demonstrated that the development, persistence, and recurrence of AF were associated with higher concentrations of proinflammatory cytokines or C-reactive protein (CRP) (12). The use of non-channel blocking drugs, which have antioxidant and anti-inflammatory properties, are recommended for AF due to its association with inflammation and oxidative stress (13). There is an important interaction between race and serum uric acid in the development of AF.

2. Objectives

To date, there has been little research on uric acid levels in patients with AF. Thus, in this cross-sectional study, we sought to investigate the association between serum uric acid levels and AF.

3. Patients and Methods

The study population consisted of patients who had no cardiovascular conditions or significant comorbidities that markedly affected levels of serum uric acid.

In this observational study, consecutive patients with persistent, permanent, or paroxysmal AF who attended the outpatient cardiology clinic or the emergency department of Shahid Beheshti hospital, Qom, Iran were recruited. The control group consisted of consecutive individuals, with no history of arrhythmias who were undergoing a regular routine clinical examination. The control group was matched for age, gender, hypertension, and diabetes.

Informed consent was obtained from all the patients, and the study was performed in accordance with the declaration of Helsinki and approved by the institutional (Qom University of Medical Sciences) ethics committee.

The diagnosis of AF was based on an electrocardiogram and confirmed by a cardiologist.

The exclusion criteria were a history of coronary artery or valvular heart disease, thyroid dysfunction, congestive heart failure, renal failure, recent infection, malignancies, or blood dyscrasias. All baseline demographic and clinical characteristics were carefully recorded. Patients receiving diuretics, allopurinol, salicylates, or other drugs that could interfere with uric acid metabolism were also excluded.

The fasting plasma uric acid level was measured using an uricase enzymatic test, with a Zist Shimi kit. The normal range was 3.5 - 7.5 mg/dL for men and 2.4 - 5.7 mg/dL for women.

3.1. Statistical Analysis

Differences in the quantitative characteristics between the groups were evaluated using the Student's t-test. A Chi-square test was used to evaluate differences in categorical variables between the study groups.

4. Results

The final study population consisted of 32 patients with AF and 32 controls. The mean (range) age of the AF group was 69.12 (46 - 87) years, and it was 67.75 (41 - 87) years in the healthy control group (P = 0.925)

There were no statistically significant differences between the two groups in the following parameters: gender (P = 0.599), age (P = 0.925), body mass index (BMI) (P = 0.685), diabetes (P = 0.609), and hypertension (P = 0.599) (Table 1).

Table 1. Comparison of the Baseline Characteristics Between the Groups

	AF Group	Non-AF Group	Sig
Gender			0.599
Male	14	14	
Female	18	18	
Age, y	69.12	67.75	0.925
BMI, kg/m^2	26.54	26.93	0.685
History of hypertension[a]	18 (56.3)	18 (56.3)	0.599
History of diabetes[a]	9 (28.1)	9 (28.1)	0.609

[a]Values are expressed as No. (%).

The mean serum uric acid in the AF group was 5.79 $\pm$ 1.19 mg/dL compared with 4.81 $\pm$ 1.26 mg/dL in the control group, and the difference was statistically significant (P = 0.002).

5. Discussion

A large body of evidence indicates that electrophysiological and structural remodeling of the atria plays an important role in the development and perpetuation of AF. Several studies suggested that oxidative stress and inflammation seemed to be involved in the pathophysiology of AF. However, whether these processes are the cause or consequence of AF remains to be determined (14, 15).

In particular, CRP and other inflammatory markers appear to be related to left atrial enlargement, AF persistence, future AF development, and recurrence after cardioversion. One study showed that elevated concentrations of interleukin-6 and CRP were associated with higher uric acid levels (14). Recently, two small studies also reported an association between AF and serum uric acid levels. One study compared serum uric acid levels in 86 patients with paroxysmal and permanent AF with those of 48 control subjects (14). That study demonstrated stepwise increases in serum uric acid in those with a higher AF burden. It also reported that serum uric acid was positively correlated with the LA diameter.

A recent study showed that uric acid had a direct effect on endothelial dysfunction and smooth muscle cell proliferation (16). Another indicated that the serum uric acid level was closely associated with elevated levels of some inflammatory markers, such as CRP (17). Although increases in uric acid may be attributed to various pathological conditions associated with AF, multiple risk factors for AF have been identified. These include chronic renal failure, diabetes mellitus, hypertension, and cardiovascular diseases.

In hypertension, because of the decrease in renal blood flow, which stimulates urate reabsorption, the level of serum uric acid is frequently increased. On the other hand, in chronic kidney disease, uric acid increases because of the decrease in renal urate excretion. In the present study, there were no statistically significant differences between the two groups in the following parameters: gender, age, diabetes, and hypertension. Whether the elevated uric acid level found in the present study was a cause or a consequence of AF remains unclear, as this was a cross-sectional study. To shed light on this issue, the results should be confirmed in prospective cohort studies.

A previous study used the uricase-peroxidase method to measure the serum uric acid levels of individuals at baseline (18). The study population consisted of 15,382 initially AF-free men and women aged 45 - 64, who were participants in the ARIC study, which followed up patients from 1987 to 2004. AF was ascertained using hospital records and electrocardiograms performed during follow-up. The unadjusted incidence of AF increased from three per 1000 person-years in the first quartile of serum uric acid to eight per 1000 person-years in quartile 4 of serum uric acid. Cox proportional models were adjusted simultaneously for age, sex, race, systolic and diastolic blood pressure, serum glucose, body mass index, LDL, prevalent coronary heart disease and heart failure, creatinine, use of diuretics, and the p wave duration on the ECG at baseline. When compared to subjects in the lowest quartile, the hazard ratio of AF for subjects in the highest quartile of serum uric acid was 1.38 (95% CI 1.07 - 1.80).

In the present study, we reported an independent association between increased levels of uric acid and AF. However, some potential limitations should be considered. First, oxidative stress markers were not assessed. Second, patients with paroxysmal, persistent, and permanent AF were not analyzed separately. Third, as this was a cross-sectional study, it remains unclear whether the elevation in the uric acid level was a cause or consequence of AF. Further larger studies, with a long-term follow-up are needed to elucidate the exact pathophysiological and prognostic role of uric acid levels in this setting. Further studies are also needed to shed light on the role of uric acid-lowering agents as upstream therapy in AF.

References

1. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. *N Engl J Med.* 2008;**359**(17):1811–21. doi: 10.1056/NEJMra0800885. [PubMed: 18946066].
2. Watanabe E. Uric acid and atrial fibrillation - cause or other association?. *Circ J.* 2012;**76**(3):584–5. [PubMed: 22293454].
3. Wu XW, Muzny DM, Lee CC, Caskey CT. Two independent mutational events in the loss of urate oxidase during hominoid evolution. *J Mol Evol.* 1992;**34**(1):78–84. [PubMed: 1556746].
4. Hediger MA, Johnson RJ, Miyazaki H, Endou H. Molecular physiology of urate transport. *Physiology (Bethesda).* 2005;**20**:125–33. doi: 10.1152/physiol.00039.2004. [PubMed: 15772301].
5. 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 U S A.* 1981;**78**(11):6858–62. [PubMed: 6947260].
6. Waring WS, Convery A, Mishra V, Shenkin A, Webb DJ, Maxwell SR. Uric acid reduces exercise-induced oxidative stress in healthy adults. *Clin Sci (Lond).* 2003;**105**(4):425–30. doi: 10.1042/CS20030149. [PubMed: 12801243].
7. Wyngaarden JB, Kelley WN. Gout and hyperuricemia. Grune and Stratton; 1976.
8. 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. [PubMed: 10391820].
9. Hoieggen A, Alderman MH, Kjeldsen SE, Julius S, Devereux RB, De Faire U, et al. The impact of serum uric acid on cardiovascular outcomes in the LIFE study. *Kidney Int.* 2004;**65**(3):1041–9. doi: 10.1111/j.1523-1755.2004.00484.x. [PubMed: 14871425].
10. Khoo CW, Krishnamoorthy S, Lim HS, Lip GY. Atrial fibrillation, arrhythmia burden and thrombogenesis. *Int J Cardiol.* 2012;**157**(3):318–23. doi: 10.1016/j.ijcard.2011.06.088. [PubMed: 21726909].
11. Yamashita T, Sekiguchi A, Iwasaki YK, Date T, Sagara K, Tanabe H, et al. Recruitment of immune cells across atrial endocardium in human atrial fibrillation. *Circ J.* 2010;**74**(2):262–70. [PubMed: 20009387].
12. Watanabe E, Arakawa T, Uchiyama T, Kodama I, Hishida H. High-sensitivity C-reactive protein is predictive of successful cardioversion for atrial fibrillation and maintenance of sinus rhythm after conversion. *Int J Cardiol.* 2006;**108**(3):346–53. doi: 10.1016/j.ijcard.2005.05.021. [PubMed: 15964643].
13. Liu T, Li L, Korantzopoulos P, Liu E, Li G. Statin use and development of atrial fibrillation: a systematic review and meta-analysis of randomized clinical trials and observational studies. *Int J Cardiol.* 2008;**126**(2):160–70. doi: 10.1016/j.ijcard.2007.07.137. [PubMed: 18031847].

14. Letsas KP, Korantzopoulos P, Filippatos GS, Mihas CC, Markou V, Gavrielatos G, et al. Uric acid elevation in atrial fibrillation. *Hellenic J Cardiol.* 2010;**51**(3):209–13. [PubMed: 20515852].
15. Celik M, Yalcinkaya E, Yuksel UC, Gokoglan Y, Bugan B, Kabul HK, et al. Increased serum uric acid levels are correlated with decreased left atrial appendage peak flow velocity in patients with atrial fibrillation. *Med Princ Pract.* 2015;**24**(3):263–8. doi: 10.1159/000373892. [PubMed: 25676205].
16. Kang DH, Park SK, Lee IK, Johnson RJ. Uric acid-induced C-reactive protein expression: implication on cell proliferation and nitric oxide production of human vascular cells. *J Am Soc Nephrol.* 2005;**16**(12):3553–62. doi: 10.1681/ASN.2005050572. [PubMed: 16251237].
17. Ruggiero C, Cherubini A, Miller E 3rd, Maggio M, Najjar SS, Lauretani F, et al. Usefulness of uric acid to predict changes in C-reactive protein and interleukin-6 in 3-year period in Italians aged 21 to 98 years. *Am J Cardiol.* 2007;**100**(1):115–21. doi: 10.1016/j.amjcard.2007.02.065. [PubMed: 17599452].
18. Tamariz L, Agarwal S, Soliman EZ, Chamberlain AM, Prineas R, Folsom AR, et al. Association of serum uric acid with incident atrial fibrillation (from the Atherosclerosis Risk in Communities [ARIC] study). *Am J Cardiol.* 2011;**108**(9):1272–6. doi: 10.1016/j.amjcard.2011.06.043. [PubMed: 21855838].