Original Paper

Serum Uric Acid Is Not an Independent Risk Factor for Premature Coronary Artery Disease

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Key Words

Premature coronary artery disease · Uric acid · Cardiovascular risk factor · Coronary angiography

Abstract

Background/Aim: There is still debate on the role of serum uric acid as an independent risk factor for coronary artery disease (CAD), particularly premature CAD. This study aimed to investigate whether serum uric acid is a risk factor for premature CAD and whether it can influence the severity of coronary artery stenosis. **Methods:** Candidates for coronary artery angiography (age <45 years for men and <55 years for women) who met the inclusion criteria were enrolled in this study. Clinical data of the patients as well as their serum uric acid levels were compared with the presence of premature CAD. **Results:** In total, 473 patients were included and divided into two groups: the premature CAD group consisted of 245 patients (age = 46.2 ± 5.7 years; males = 110, 44.9%) and the normal coronary group consisted of 228 subjects (age = 45.7 ± 6.4 years; males = 62, 27.2%). Uric acid was significantly related to the presence of CAD, but this relationship was not significant after adjustment for confounding variables, including classic CAD risk factors. CAD patients were then categorized based on the extent of the disease (from minimal CAD to three-vessel disease); however, unlike the classic risk factors of CAD, uric acid was not significantly different between these groups ($p = 0.10$), and a similar result was observed after adjustment for confounders. **Conclusion:** Uric acid is not an independent risk factor for premature CAD but is weakly correlated with the extent of the disease; nevertheless, this relationship requires further investigation.

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Introduction

Cardiovascular diseases are still the leading cause of death in the world despite improvements in medical management and technology. The growing number of elderly people is accompanied by an increase in the number of people affected by cardiovascular diseases [1]. Therefore, the preventable nature of cardiovascular diseases, especially coronary artery disease (CAD), underscores the need for an early recognition of the disease and its risk factors [2]. Until now, several risk factors for CAD have been identified [3, 4]; however, there are still other controversial factors that demand further studies so they can be consolidated as definite risk factors for premature CAD, among which uric acid could be a useful clinical biomarker.

Serum uric acid, the final product of purine metabolism, has been shown to be correlated with cardiovascular diseases. It has also been suggested as a predictor of mortality and morbidity in patients with cardiovascular disorders such as hypertension [5], myocardial infarction [6], and congestive heart failure [7]. Although some studies have proposed uric acid as a cardiovascular risk factor [8], this claim is still controversial and needs to be elucidated. Moreover, data about the role of uric acid as a cardiovascular risk factor in otherwise healthy young subjects, particularly those with premature CAD, are scarce as there may be differences between classic atherosclerosis and premature atherosclerosis.

In this study, we aimed to investigate whether serum uric acid is a risk factor for premature CAD and whether it can influence the severity of coronary artery stenosis as measured by the Gensini score and the clinical vessel score based on coronary angiography results.

Methods

This retrospective study included candidates for coronary artery angiography due to unstable angina who attended the Tehran Heart Center between April 2010 and September 2012 and who were eligible to enter the study based on the defined protocol. Our inclusion criteria were: age <45 years for men and <55 years for women, no history of renal disease or gout, no history of any malignancy, rheumatologic, renal, or hepatic disease, and a negative history for the use of diuretics or uric acid-modifying agents. Written informed consent was obtained from each patient, and the study protocol was approved by the Institutional Research Board and Ethical Committee.

Baseline demographics, past medical history, family history of CAD, laboratory measurements, and clinical and angiographic characteristics were recorded for each subject at admission and were later retrieved from the database of our center. After an overnight fasting, venous blood samples were obtained on the day of the procedure in order to measure serum uric acid, fasting blood sugar, and lipid profile. Serum uric acid was measured with commercially available kits via the colorimetric assay method using the Cobas Integra® 400 analyzer (Roche Diagnostics Ltd., Switzerland). Reference values for uric acid were 4.0–8.0 mg/dl in men and 3.0–7.0 mg/dl in women.

The presence of premature CAD was confirmed by conventional angiography. Coronary artery angiography was performed at the catheterization laboratory of Tehran Heart Center under local anesthesia by an expert cardiologist, and the results were interpreted by two other cardiologists blinded to the study protocol. Based on these results, the subjects were then divided into two groups: the normal coronary group and the premature CAD group. CAD was classified based on the clinical vessel score [9] and the Gensini score [10]. With the clinical vessel score, the patients were categorized as having single-vessel, two-vessel, or three-vessel disease. The Gensini score was calculated by assigning a severity score to each coronary stenosis regarding the degree of luminal narrowing and the importance of its location. The decrease in the lumen diameter and the roentgenographic appearance of concentric lesions and eccentric plaques were evaluated (reductions of 25, 50, 75, 90, and 99%, and complete occlusion were given the Gensini scores of 1, 2, 4, 8, 16, and 32, respectively). Each principal vascular segment was assigned a multiplier in accordance with the functional significance of the myocardial area supplied by that segment: the left main coronary artery, $\times 5$; the proximal segment of the left anterior descending coronary artery and the proximal segment of the circumflex artery, $\times 2.5$; the mid-segment of the left anterior descending coronary artery, $\times 1.5$; the right coronary artery, the distal segment of the left anterior descending coronary artery, the distal segment of the circumflex artery,

Table 1. Clinical characteristics of the study population and gender-based subgroups with normal coronary arteries (group 1) and premature CAD (group 2)

Characteristics	Total population (n = 473)		p value
	group 1 (n = 228)	group 2 (n = 245)	
Male gender	62 (27.2)	110 (44.9)	<0.001
Age, years	45.7±6.4	46.2±5.7	0.33
BMI	29.3±4.7	29.5±5.4	0.76
Family history of CAD	44 (19.6)	85 (35.4)	<0.001
Diabetes mellitus	50 (21.9)	86 (35.1)	0.001
Hypertension	86 (37.7)	133 (54.5)	<0.001
Dyslipidemia	142 (62.8)	198 (80.8)	<0.001
Smoking	35 (15.3)	85 (34.7)	<0.001
Opium use	12 (5.5)	17 (7.5)	0.35
FBS, mg/dl	110.4±35.0	135.5±63.1	0.001
Total cholesterol, mg/dl	182.1±41.9	194.4±59.1	0.01
HDL, mg/dl	44.3±11.0	39.9±10.8	<0.001
LDL, mg/dl	107.6±38.2	115.1±45.8	0.06
Triglyceride, mg/dl	171.2±118.2	219.4±196.9	0.002
Creatinine, mg/dl	0.9±0.2	1.0±0.8	0.19
Ejection fraction, %	53.0±11.9	51.7±10.9	0.25

Values represent n (%) or mean ± SD. FBS = Fasting blood sugar; HDL = high-density lipoprotein; LDL = low-density lipoprotein. p < 0.05 was considered significant.

the right coronary artery, the posterolateral artery, the posterior descending artery, and the obtuse marginal artery, ×1; and the diagonal artery and others, ×0.5. Patients with a normal angiography were classified as the control group, and their Gensini score was considered zero.

Statistical Analysis

Continuous variables are given as means ± SD and were compared between the normal coronary and premature CAD groups using the independent sample t test for normally distributed variables, while the one-way analysis of variance (ANOVA) was used to compare them between the normal, minimal CAD, one-vessel disease, two-vessel disease, and three-vessel disease groups or in case the variables were not normally distributed. Categorical variables are given as frequency (percentage) and were compared between the groups mentioned above using a χ^2 test. A logistic regression model was used to adjust the relationship between serum uric acid and premature CAD with respect to gender, diabetes mellitus, dyslipidemia, cigarette smoking, opium addiction, and creatinine level. The cumulative logit model was used to evaluate the relationship between serum uric acid and the extent of CAD adjusted in terms of gender, dyslipidemia, opium addiction, diabetes mellitus, cigarette smoking, age, and ejection fraction as possible confounders. Analyses were performed using the PASW® statistical software for Windows, version 18 (SPSS Inc., Chicago, Ill., USA). A p value ≤0.05 was considered statistically significant.

Results

From a total of 20,041 patients who underwent diagnostic coronary angiography at the Tehran Heart Center within the study period, 3,852 cases were premature CAD patients. For this study, a sample size of 473 patients meeting our inclusion criteria was selected. The recruited patients were then divided into two groups based on the results of their angiography. A sum of 228 patients with normal coronary arteries and 245 patients with premature CAD were then compared for their baseline characteristics, as is shown in table 1. The serum uric acid levels in the premature CAD group were significantly higher than those in the

Fig. 1. Comparison of the level of serum uric acid between the normal coronary subjects and premature CAD patients in the study population (a), men (b) and women (c) (data shown as mean ± SD).

subjects with normal coronary arteries (6.50 ± 1.92 vs. 6.11 ± 1.74 mg/dl; $p = 0.02$); however, when comparing men and women separately for uric acid, there was no significant difference between the groups (fig. 1).

Serum uric acid was subsequently adjusted for confounding variables, including gender, family history of CAD, diabetes mellitus, hypertension, dyslipidemia, smoking, and opium use as well as levels of fasting blood sugar, total cholesterol, triglyceride, and serum creatinine (table 2). Nevertheless, there was no relationship between the serum level of uric acid and the presence of premature CAD ($p = 0.94$).

In order to examine the relationship between serum uric acid and the extent of CAD, the premature CAD patients were divided into four subgroups based on the vessel score (from minimal CAD to three-vessel disease), and the study variables were then compared between the groups (table 3). In this model, there was no significant difference between the groups regarding uric acid levels ($p = 0.1$), despite the fact that classic risk factors for CAD, i.e. family history of CAD, diabetes mellitus, hypertension, dyslipidemia, and smoking, were significantly related to the extent of the disease ($p = 0.001$, $p < 0.001$, $p < 0.001$, $p = 0.001$, and $p < 0.001$, respectively). After adjustment for the confounding variables, the relationship of serum uric acid with the extent of CAD was not meaningful ($p = 0.25$). The correlation between uric acid level and Gensini score was also tested, and a weak correlation was observed (Spearman's correlation = 0.01, $p = 0.02$).

Discussion

In the present study, we aimed to assess the association between serum uric acid levels and the presence and severity of premature CAD based on the results of coronary angiographies. Our findings show that despite the initial difference in the levels of serum uric acid between the two groups, this relationship disappeared after adjustment for confounding variables, including classic risk factors for CAD. In addition, there was no correlation between serum uric acid level and CAD severity regarding the vessel score and Gensini score.

Several studies have been performed to investigate the relationship between serum uric acid and different aspects of cardiovascular diseases. It is well documented that uric acid is related to risk factors for CAD such as hypertension [5, 11–13], diabetes mellitus [14], meta-

Table 2. Adjusted effect of the variables on the presence of CAD

Characteristics	Odds ratio	95% CI	p value
Male gender	0.49	0.21–1.15	0.1
Family history of CAD	4.43	1.73–11.33	0.002
Diabetes mellitus	2.06	0.77–5.51	0.15
Hypertension	2.21	1.10–4.43	0.02
Dyslipidemia	2.26	0.99–5.20	0.05
Smoking	4.92	1.40–17.25	0.01
Opium use	0.28	0.05–1.43	0.12
FBS	1	0.99–1.01	0.16
Total cholesterol	1	0.99–1.00	0.54
Triglyceride	0.99	0.99–1.00	0.56
Creatinine	0.95	0.56–1.64	0.87
Uric acid	0.99	0.77–1.27	0.94

FBS = Fasting blood sugar. $p \leq 0.05$ was considered significant.

Table 3. Comparison of the study variables based on the vessel score subgroups

Characteristics	Normal	Minimal CAD	Single-vessel disease	Double-vessel disease	Triple-vessel disease	p value
Male gender	45 (24.9)	17 (36.2)	48 (49.5)	32 (50.8)	30 (35.3)	<0.001
Age, years	45.27±6.63	47.40±5.40	45.75±6.15	45.87±5.76	47.09±5.30	0.16
BMI	29.22±4.7	29.89±4.78	29.14±6.49	29.74±4.72	29.74±4.75	0.47
Family history of CAD	36 (19.8)	8 (17.0)	30 (31.9)	27 (42.8)	28 (32.9)	0.001
Diabetes mellitus	33 (18.2)	17 (36.2)	28 (28.9)	20 (31.7)	38 (44.7)	<0.001
Hypertension	61 (33.7)	25 (53.2)	42 (43.2)	37 (58.7)	54 (63.5)	<0.001
Dyslipidemia	113 (62.4)	29 (61.7)	79 (81.4)	51 (81.0)	51 (81.0)	0.001
Smoking	18 (9.9)	3 (6.4)	32 (33.0)	16 (25.4)	15 (17.6)	<0.001
Opium use	12 (6.6)	4 (8.5)	9 (9.2)	9 (14.2)	5 (5.8)	0.19
FBS, mg/dl	107.34±25.33	119.13±53.45	120.85±49.79	142.45±60.57	146.84±74.98	0.01
Total cholesterol, mg/dl	181.56±41.31	184.13±44.77	186.88±53.18	196.12±58.91	201.82±65.02	0.14
HDL, mg/dl	44.12±10.74	45.26±12.06	40.15±10.85	40.93±11.64	39.00±10.45	<0.001
LDL, mg/dl	107.18±37.11	109.26±42.67	109.88±39.81	119.89±51.98	117.82±47.63	0.51
Triglyceride, mg/dl	172.02±125.28	168.23±88.72	190.40±108.61	211.97±102.52	257.52±295.89	0.01
Creatinine, mg/dl	0.99±0.25	0.96±0.22	0.95±0.23	0.99±0.25	1.23±1.40	0.53
Ejection fraction, %	54.13±11.76	48.78±11.94	51.51±11.01	52.92±11.20	50.99±10.71	0.03
Uric acid, mg/dl	6.15±1.74	5.93±1.74	6.49±1.83	6.63±2.08	6.40±1.92	0.1

Values represent n (%) or mean ± SD. FBS = Fasting blood sugar; HDL = high-density lipoprotein; LDL = low-density lipoprotein. $p \leq 0.05$ was considered significant.

bolic syndrome [15, 16], dyslipidemia [17], and obesity [18, 19]. One study demonstrated that hyperuricemia was significantly associated with the extent and severity of CAD in patients with a mean age of around 60 years [8]. Contrary to this, the findings of the Framingham study showed no causal role between uric acid and the development of CAD as well as cardiac-related death and even all-cause mortality [20]. Further, a similar finding was observed in the ARIC study that did not recognize uric acid as an independent risk factor for coronary heart disease [21]. On the other hand, uric acid could independently predict cardiovascular mortality in patients with angiographically proven CAD [22, 23]. However, there are still discrepancies regarding the contributing role of uric acid in the onset or aggravation of premature CAD. It

should also be noted that several risk factors, including genetic predisposition, intervene in the development of premature CAD [24], and that premature CAD may have a different nature from CAD in later life.

Hyperuricemia has been shown to be associated with endothelial dysfunction, and decreased nitric oxide bioavailability has been proposed as the main cause for this dysfunction [25, 26]. Besides, several studies have recognized the serum uric acid levels as predictors for critical cardiovascular events, particularly myocardial infarction [20, 27–30]. However, these findings were not comprehensive enough to rationalize the role of uric acid as an independent risk factor for CAD as the subjects with CAD in previous studies had a worse state of classic cardiovascular risk factors, particularly metabolic indices such as the body mass index (BMI) and lipid profile. In the present study, serum uric acid levels were initially higher in the premature CAD group, but the disappearance of this association after adjustment for confounding variables can clearly explain how uric acid levels can alter secondary to other classic risk factors for CAD. Similarly, a significant correlation between serum uric acid and several risk factors for CAD has been demonstrated, and uric acid has not been independently associated with the presence and severity of CAD [15]. A study on a large Chinese population found that serum uric acid levels were significantly associated with central arterial stiffness independent of conventional cardiovascular risk factors such as sex, BMI, lipids, and glucose metabolism, while there was no association with peripheral arterial stiffness [31]. On the other hand, significant interactions between serum uric acid and heart rate or blood pressure were observed. This can confirm our hypothesis that the rise in serum uric acid and the development of CAD are parts of a vicious cycle created by atherosclerotic risk factors.

In our study population, serum levels of uric acid were significantly higher in men, which is in line with results from other studies [22]. It has also been demonstrated that serum uric acid levels predicted cardiovascular events in male patients with CAD, and only the highest uric acid quartile was a predictor of cardiovascular events in women [32]. However, there was no relationship between uric acid and premature CAD within each gender group in the present study. Therefore, it seems that the elevation in serum uric acid levels later in the course of the disease and its synergistic effect with other cardiovascular risk factors can augment the severity of atherosclerosis and lead to cardiovascular events. It should also be noted that premature CAD and thereby premature atherosclerosis may comprise different pathogeneses, such as genetic predisposition, compared to the classic atherosclerosis, and thereby the role of uric acid as a risk factor for premature CAD may be influenced by some unknown factors.

The present study has some limitations. The first limitation is that we only measured serum uric acid right before the angiography. A cohort design with the capability of tracking the changes of serum uric acid could better show the impact of uric acid on the process of atherosclerosis and development of premature CAD. Another possible limitation is the selection bias as the Tehran Heart Center is a tertiary referral hospital. Consequently, our study population did not necessarily represent the general population. The sample size of the study could also have influenced the findings, and maybe a larger sample size can improve the power of the study.

Conclusion

In this study, we did not observe an independent relationship between serum uric acid levels and the presence of premature CAD, although there was a weak correlation with disease severity. Based on our findings and the body of literature, it seems that uric acid is not a strong and independent risk factor for premature atherosclerosis, which is consistent

with the findings of larger studies on CAD patients. Future longitudinal studies with larger sample sizes can help to identify the exact role of uric acid in the course of coronary atherosclerosis.

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