



## Determination of the Association between Uric Acid Level and Intensity of Coronary Artery Diseases

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### ABSTRACT

Some evidences prove that uric acid level is not a risk factor for heart diseases, but oppositely, some community-based studies point to uric acid as a risk factor of occurrence of cardiovascular diseases. This study evaluates the correlation between these two issues in Iran, which has a high prevalence. In this cross-sectional study, 300 patients who were candidates of CAD were studied. The blood was taken from the patients to do routine tests such as FBS and lipid profile. The blood uric acid level was determined. Angiography of coronary blood was performed after 12 hours of fast. The total serum level of uric acid of all the patients was  $5.15 \pm 1.47$  mg/dl which for men it was  $5.27 \pm 1.48$  mg/dl and it was significantly higher than the same parameter for women ( $4.88 \pm 1.43$  mg/dl) ( $P$ -Value= 0.035). The correlation between the serum uric acid level and the LVEF did not show any significant relationship ( $P$ -Value= 0.161). Smoking, hypertension, diabetes, or hyperlipidemia did not influence the blood uric acid level. There was no significant relationship between the serum uric acid level and the number of involved coronary blood artery; however, the serum uric acid level in the patients with the left main involvement was significantly higher than patients without it ( $P$ -Value=0.018). In the multivariable logistic regression statistical model, the serum uric acid level is considered as an index in prediction of left main involvement beside other to-be-studied parameters such as sex, age, cardiac risk factors, LVEF level, and serum creatinine level. Increased levels of uric acid is related to the risk factor of left main occurrence dependably from other heart health risk factors such as hyperlipidemia, hypertension, and diabetes. But probably increased level of uric acid has no relationship with involved coronary blood artery.

**Keywords:** Uric Acid, Coronary Artery Diseases.

### INTRODUCTION

The correlation between increased blood uric acid and cardiovascular diseases was unknown until 1950 and beginning of 1960. In 1960, first evidences of increased cardiovascular risk factor because of increased uric acid levels and related diseases were presented [1-3]. Some epidemiologic studies showed that there is a significant relationship between uric acid levels and some factors influencing the cardiovascular disorders such as hypertension [1], metabolic syndrome [4], coronary blood artery [5], cerebrovascular diseases [6], vascular dementia [7], pre-eclampsia [8], and renal diseases [9, 10]. Increased uric acid levels in cardiovascular disorders might be started because of other processes such as decreased glomerular filtration, hyperuricemia contraction of renal vessels, prescription of diuretics, drinking alcohol, tissue ischemia, or oxidative stress process [11-13]. The association between the level of uric acid and occurrence and intensity of cardiovascular diseases is still unknown. Some evidences such as the study of Framingham and colleagues demonstrated that high blood uric acid is not a risk factor for occurrence of cardiovascular disorders and it is suggested to the specialists to control the classic risk factors for cardiovascular disorders [14]. Oppositely, some community-based studies mention high uric acid as one of important risk factors for occurrence and intensity of cardiovascular disorders [15, 16]. One of the problematic

issues in assessment of the dangerous correlation among the uric acid levels and cardiovascular diseases is that the uric acid itself is in correlation with some classic risk factors of cardiovascular disorders. For instance, the uric acid levels is significantly higher in some high-risk substrates of cardiovascular diseases such as women after the menopause, black people, patients with hypertension, patients with metabolic syndrome, and patients with heart failure. In the case of the role of uric acid in cardiovascular diseases, epidemiologists have implemented multi-regression studies often, to evaluate the presence of relationship of high blood uric acid and cardiovascular diseases in cases in which there are risk factors of cardiovascular diseases. Having this appeal, some studies demonstrated that the relationship of high blood uric acid and developing the cardiovascular diseases is not independent from other risk factors of cardiovascular diseases [17-19]. Consequently, controlling the uric acid without controlling other risk factors levels is not effective in controlling cardiovascular diseases. Some other studies persisted on the preventing effect of uric acid on the intensity of cardiovascular diseases and declared that one of the effective prevention mechanisms of uric acid is its role as antioxidant [11, 20]. Studies on animal samples and cell culture have presented some mechanisms which demonstrate the probable relationship between blood uric acid levels with renal or cardiovascular diseases [21-23]. Also in some recent clinical trials, the effect of reduction of uric acid on prevention and even therapy of renal or cardiovascular diseases have been proven [9, 10, 24, 25]. Considering the mentioned evidences based on animal experiments and clinical trials, obviously still the relationship between level of uric acid and occurrence and intensity of cardiovascular diseases is doubted. On the one hand, there are evidences proving the relationship of level of uric acid and risk factors of cardiovascular diseases, and on the other hand the antioxidant effect of uric acid states its preventing role in cardiovascular diseases. Many studies did not find any relationship between level of uric acid and cardiovascular diseases. On the other hand, some seek the relationship between level of uric acid and cardiovascular diseases among the genetic and geographic differences. Therefore, we decided to study the association between level of uric acid and cardiovascular diseases in Iran which has a high prevalence especially among young people.

#### MATERIALS AND METHODS

In this cross sectional study, 30 patients who were candidates of angiography for different reasons such as ribcage pain or exercise test or disordered perfusion scan were brought into the study regarding medical ethic principals. The excluding criteria were as below: a) Acute Coronary Syndrome (ACS) history within the three months ending the angiography of coronary arteries, b) Diabetes history or therapy with hypoglycemic medications, c) Random blood sugar higher than 200 mg/dl while reference to the doctor, d) Fast Blood Sugar (FBS) more than or equal to 126 mg/dl either while reference to the doctor or while recent examinations, e) Renal function disorders (serum cr >1.5 mg/dl), f) Hepatic or pulmonary dysfunction or thyroid symptomatic diseases, g) Taking high dosages of corticosteroids, diuretics, antioxidants or alcohol history, h) Coronary Artery Bypass Grafting (CABG) or Percutaneous Coronary Intervention (PCI) history, i) Cardiomyopathy diseases.

Blood samples were taken from the patients who were brought into the study in order to implementation of routine examinations such as FBS and lipid profile. Moreover, the serum uric acid test was done with the enzymatic calorimetric approach by uricase and peroxidase enzymes. Angiography of coronary arteries was done according to the standard femoral approach after 12 hours of fast by the cardiologist who was not informed about clinical and laboratory conditions of patients. The intensity of coronary artery disease was sorted based on angiography information and number of more than 50% involvement of arteries as below: i) Normal coronary, ii) One vessel disease, iii) Two vessel disease, iv) Three vessel disease.

Also, the left coronary involvement determined and registered as left main lesion. The obtained results were expressed as standard deviation and average (mean±SD) for quantitative variables and as percentage for qualitative and sorted variables. Comparison of two groups was done with either T-test or Mann-Whitney test. Qualitative variables comparison was done using either Chi-square test or precise Fischer test. ANOVA test was used to evaluate the difference of the levels of uric acid based on involvement rate of coronary arteries. The correlation between occurrence of either the CAD or the left main lesion and uric acid levels was assessed in presence of study confounders such as demographic agents and risk factors of cardiovascular diseases using the logistic multivariable regression analysis. The results were reported as likelihood ratio and confidence interval of 95% for likelihood ratio. The area under the ROC curve was used to determine the prediction value of uric acid for diagnosis of coronary diseases from normal conditions. The significant level was considered lower than 0.05. The SPSS ver.15 and SAS ver.9.1 were used to statistical analysis of the data.

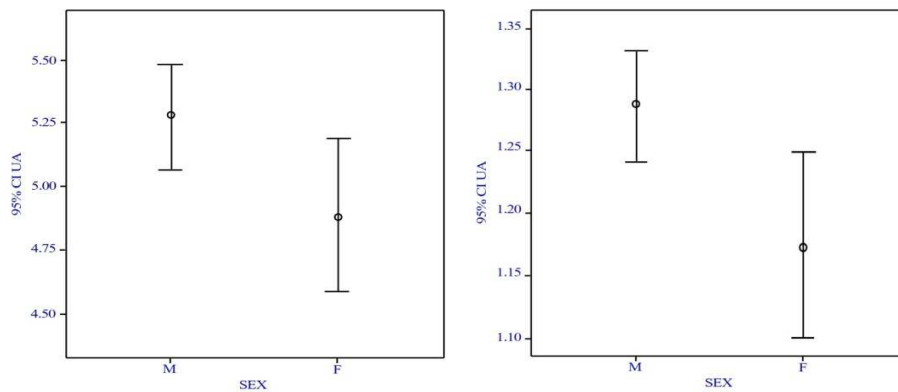
**RESULTS**

300 patients were evaluated in this study. 207 patients (69%) were male and 93 patients (31%) were female. The total age average of the patients is  $57.30 \pm 11.07$  (ages from 33-84 years old). Following results are reported regarding cardiovascular risk factors: systolic hypertension in 44%, recent smoke in 29.3%, mellitus diabetes in 21%, and hyperlipidemia in 23.3% of the patients. The average of Left Ventricular Ejection Fraction (LVEF) in the patients was  $43.0 \pm 7.66\%$ . One coronary artery involvement was reported in one person (0.3%), two coronary artery involvements was reported in 195 persons (65.0%) and three coronary artery involvements was reported in 104 persons (34.7%). The prevalence of the number of involved coronary arteries had no significant difference between males and females. Left main involvement was observed in a large portion of patients, means 60 patients (20%). The left main involvement was 21.3% for males and 18.3% for females and did not show a significant difference (P-Value>0.05). The results showed that considering the general properties and prevalence of cardiovascular diseases risk factors in males and females, in the age variable, male patients were significantly younger than female patients. Also the prevalence of smoking was significantly higher in males comparing to females. There were no significant differences considering prevalence of hypertension and hyperlipidemia for both genders (Table 1).

**Table 1- General properties and cardiovascular diseases risk factors in males and females**

		Sex		P-Value
		Male	Female	
Age		$55.74 \pm 8.10$	$60.78 \pm 10.87$	< 0.001
Risk Factors	Smoking	70 (% 33.8)	18 (% 19.4)	0.011
	Systolic Hypertension	85 (% 41.1)	38 (% 40.9)	0.974
	Diabetes Mellitus	36 (% 17.4)	27 (% 29.0)	0.022
	Hyperlipidemia	51 (% 24.6)	19 (% 20.4)	0.426

In the comparison of cardiovascular conditions between males and females, the LVEF average was  $42.49 \pm 8.17\%$  for males and  $44.14 \pm 6.28\%$  for females, which this difference was not statistically significant. Serum uric acid level was totally  $5.15 \pm 1.47$  mg/dl which was  $5.27 \pm 1.48$  mg/dl for males and  $4.88 \pm 1.43$  mg/dl for females. Statistic analysis demonstrated that the serum uric acid level in males was significantly higher than females (P-Value=0.035). The serum concentration of creatinine was  $1.25 \pm 0.34$  which was significantly higher for males comparing to females ( $1.29 \pm 0.32$  mg/dl for males and  $1.18 \pm 0.36$  mg/dl for females, P-Value=0.013) (Figure 1).



**Figure 1- Serum uric acid and creatinine concentration in studied males and females**

The results obtained from this study demonstrated that there is no significant correlation among serum uric acid level and the left ventricular ejection fraction (Pearson correlation coefficient = -0.081, P-Value=0.16). Also statistical estimations confirmed that there is no significant difference regarding substrate risk factors between blood uric acid level and cardiovascular diseases risk factors. On the other hand, smoking, hypertension, diabetes, and hyperlipidemia have no effect on uric acid levels (Table 2).

**Table 2- Uric acid levels in different substrates of risk factors**

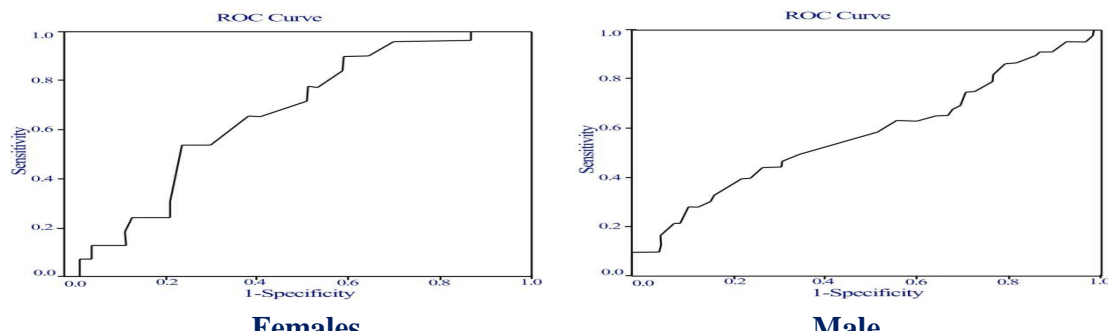
Risk Factors		Blood uric acid levels (mg/dl)	P-Value
Smoking	Yes	5.14 ± 1.39	0.741
	No	5.08 ± 1.43	
Systolic Hypertension	Yes	4.98 ± 1.53	0.250
	No	5.18 ± 1.33	
Diabetes Mellitus	Yes	5.07 ± 1.70	0.899
	No	5.10 ± 1.33	
Hyperlipidemia	Yes	5.35 ± 1.37	0.082
	No	5.02 ± 1.42	

The average of uric acid levels in patients with one involved artery (4.3±1.00 mg/dl), two involved arteries (5.08±1.44 mg/dl), and three involved arteries (5.25±1.49 mg/dl) did not show any significant difference; However, serum uric acid level in patients with left main involvement was significantly higher than patients without left main involvement (5.48±1.58 vs 5.00±1.35). In the multivariable logistic regression statistical model, the serum uric acid level is considered as an index to prediction of left main involvement in presence of other studied items such as sex, age, cardiovascular diseases, LVEF rate, and serum creatinine level (Table 3).

**Table 3- The predicting role of uric acid in the left main involvement**

Index	Likelihood ratio	Confidence interval (% 95)	P-Value
Blood uric acid levels	1.276	1.567 – 1.038	0.021
Sex	0.961	1.894 – 0.487	0.908
Age	1.016	1.045 – 0.988	0.262
Smoking	0.959	1.855 – 0.496	0.901
Systolic Hypertension	0.812	1.488 – 0.433	0.500
Diabetes Mellitus	1.226	2.560 – 0.587	0.588
Hyperlipidemia	0.609	1.319 – 0.281	0.209
LVEF	1.064	1.103 – 0.281	0.001
Serum Creatinine	1.069	2.639 – 0.435	0.884

For comparison of prediction ability of serum uric acid in prediction of left main involvement according to the ROC graph analysis, this ability is significantly higher for females (with area under the curve of 0.662) comparing to males (with area under the curve of 0.566). Totally, serum uric acid is medially capable to predict the left main lesion.



**Figure 2- Ability of uric acid in prediction of left main lesion in males and females**

**DISCUSSION**

Still there is not a unanimous opinion about hazardous or protecting effects of high levels of uric acid on cardiovascular diseases, as some studies state the relationship between hyperuricemia and high prevalence rate of cardiovascular diseases risk factors, and oppositely, some defend the preventing effect of hyperuricemia through its antioxidant effect. Some researches such as Framingham community study state no correlation among increased levels of uric acid and the intensity of cardiovascular diseases, and in fact controlling of other risk factors is

preferred to controlling the uric acid levels. What our study demonstrates is defending some and is in opposition to some other studies, as below: i] No relationship was found between risk factors of cardiovascular diseases such as hypertension, diabetes, hyperlipidemia, and smoking and the levels of blood uric acid, ii] No logical relationship was found between the number of involved coronary arteries and increased levels of uric acid, iii] There was a relationship between levels of uric acid and left main involvement, as high levels of uric acid was a principal predicting item to predict the left main coronary lesion, iv] Sex and age have no effect on correlation between the level of uric acid and cardiovascular diseases. Therefore, as it is manifest in our study, hyperuricemia is mainly related to the left main involvement in the heart rather than involvement of coronary arteries; however, the interference of hyperuricemia in left main lesion cannot be irrelevant from its interference in left main lesion. Our study can provide proved evidences of increased involvement of left main lesion followed by increased levels of uric acid. On the other hand, considering no relationship between uric acid levels and risk factors of coronary artery, the correlation between hyperuricemia and left main involvement is probably discrete from risk factors of cardiovascular diseases. Our study is unique considering some innovations. Several studies have been reported in this issue. for instance In a study done by Gur et al in 2008, the relationship between uric acid levels and coronary arteries diseases was evaluated. 495 patients with coronary diseases and 356 patients with normal coronary artery were studied to assess their angiogram. The involvement intensity of coronary artery was determined with the Gensini score. Studies demonstrated that the uric acid level was significantly higher in the patients group comparing to the control group. The prevalence of the involvement was higher in males which confirm the results of current study. In the group of patients with cardiovascular diseases there was no significant relationship between the intensity of coronary involvement and the Gensini score, therefore expectedly the levels of serum uric acid is related to presence of coronary involvement, not with the intensity of the coronary involvement [26]. The results of this study also confirm the study performed by Tatli et al. Their study was performed on 80 patients who were all under 35, who had Acute myocardial infarction according to clinical and laboratory evidences. The patients were divided into two groups. The first group had coronary diseases according to angiographic evidences and the second group had normal coronaries. The uric acid levels were compared between these two groups. Although there was no difference between these two considering the lipid profile level, risk factors of cardiovascular diseases, coagulation factors, sex, and age, but the levels of uric acid in male patients were significantly higher than females [ $7.0 \pm 1.4$  mg/dl for males versus  $4.9 \pm 1.1$  mg/dl for females] [27]. The present study proved that serum uric acid has a medium ability in prediction of left main involvement. In a similar study done by Jelic-Ivanovic et al. the surface prediction ability of uric acid was assessed. They evaluated the serum levels of uric acid and occurrence of coronary diseases in middle-aged patients. The results demonstrated that the levels of serum uric acid in the patients with coronary diseases were significantly higher than healthy people. This significant result was not restricted to the normal levels of uric acid of the serum. In the females with more than 50% of involvement even regardless the number of involved arteries, high levels of uric acid was in relationship with coronary diseases. Therefore, high levels of uric acid can be one of the important items of clinical prediction of coronary diseases [28]. Firstly, this is the first study in which the relationship between the left main lesion and uric acid levels was directly studied. Second, considering the geographic and genetic factors, this is the first study in Iran. Although, there were restrictions in this study as below: i] In this study, the numbers of involved arteries are considered but not the Gensini Score, ii] Obesity as one of the important and influencing items on uric acid levels has not been studied, iii] Consideration of bigger sample size would make a stronger study to evaluate the involvement of coronary arteries and uric acid levels.

### CONCLUSION

Totally it can be uttered that the increased levels of uric acid is accompanied by the risk of left main lesion, independently from other risk factors such as hypertension, diabetes, or hyperlipidemia. Probably the increased uric acid is not related to the number of coronary arteries. Implementation of clinical trials with lowering medication of uric acid can provide proofs for the discoveries of this study.

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