Serum Uric Acid and Its Association with Coronary Artery Disease

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Key words:
Serum uric acid, Coronary artery disease, Gensini scores, Coronary angiography

Abstract:

Background: *Few studies have assessed the relation of uric acid level with the severity of coronary artery disease (CAD). This study investigated the association between high uric acid levels with the presence and severity of CAD.*

Materials and Methods: *This study was designed as an observational cohort study. The study was composed of 180 patients admitted at our institution due to symptoms related to CAD. Patients having angiographic evidence of stenosis in coronary artery were as case group and without stenosis control group. Patients with high uric acid (hyperuricemia) were defined as serum uric acid concentration ≥7.0mg/dl or ≥420 µmol/L in men and ≥6mg/dl or ≥360 µ mol/L in women. The presence of CAD has been defined as the Gensini score being ≥1.*

Results: *There was a statistically significant difference between the mean uric acid levels of patients with and without CAD (358.23±71.11 µmol/l vs251.32±54.92 µmol/l respectively, p<0.001). There was a statistically significant difference between ejection fraction of patients with and without CAD (54.50±9.25 vs. 63.16±6.56 respectively, p<0.001). Spearman correlation analysis demonstrated a positive correlation between the serum uric acid level and the severity of CAD (p=<0.001, r=0.39). When patients were classified into four groups according to their Gensini score, mean serum uric acid level was found to be significantly increased across the tertiles, and a statistically significant difference was detected between the tertiles (p= <0.001).*

Conclusion: *In conclusion, a significant association has been found between serum uric acid level and the presence and severity of CAD. In addition to the evaluation of conventional risk factors in daily clinical practice, the measurement of uric acid level might provide significant prognostic benefits in terms of global cardiovascular risk and management of the patients.*

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Introduction:

Increased serum uric acid (SUA) levels are frequently encountered in subjects with obesity, glucose intolerance, renal disease, hyperlipidemia, athrosclerosis and hypertension which all play a causal role in the pathogenesis of coronary artery disease (CAD).[1-4] The clinical value of SUA for predicting CAD, however, is uncertain.

Several cohort studies on subjects with HTN have revealed a significant association between SUA and future cardiovascular (CV) events.[5,6] Additionally, based on data from the First National Health and Nutrition Examination Survey (NHANES1),[7] increased SUA levels are independently and significantly associated with ischemic heart disease and CV mortality. In contrast, results of the Framingham Heart Study [8] and Evans County Study,[9] which are extensively quoted epidemiology examinations, have shown that hyperuricemia cannot be recognized as an independent CV risk factor.

Uric acid is the end-product of purine catabolism. It has antioxidant properties and is responsible for scavenging of 60% of the free radicals in human serum.[10] In addition to being an effective extracellular anti oxidant, uric acid also stimulates granulocyte adhesion to endothelial cells and liberation of peroxide and superoxide free radicals.[11] A close relationship has been observed between high serum uric acid level and inflammatory markers, such as the total number of leukocytes, the number of neutrophils, C-reactive protein, interleukins and tumour necrosis factor alpha.[12-14] Uric acid acts like an antioxidant

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in the early stages of the atherosclerotic process and also is the strongest determinant of plasma antioxidant capacity.[15] High serum uric acid work this antioxidant state is paradoxically reserved into a pro-oxidant state in the later stages of the artherosclerotic process. This paradoxal state appears to be dependent on several environmental factors such as stage of the disease process, acidity of the tissues, reduction in other local antioxidants and the presence of oxidant substances and enzyme.[16]

The pathophysiologic mechanisms underlying increased SUA concentrations in atherosclerotic diseases appear to be accounted for by insulin resistance which is a major characteristic of metabolic syndrome (MS) and is strongly associated with CAD.[17] Therefore, the objective of the present study was designed to determine the relationship between serum uric acid level and the presence and severity of coronary artery disease (CAD).

Materials and Methods:

The study was composed of 280 patients, between May 2011 and February 2012, were consecutively admitted at our institution due to symptoms related to CAD. All patients had elective coronary angiography at our centre. The patients were assessed a day prior to coronary angiography and a full clinical history was obtained. This study was designed as an observational prospective cohort study. Patients having angiographic evidence of stenosis in coronary artery or major branch segment in their epicardial coronary tree were as having CAD (CAD+case group) and with out stenosis (CAD-control group). Exclusion criteria were the first 4 weeks of acute coronary syndrome, previous percutaneous coronary intervention/stent implantation and/or previous coronary artery bypass grafting, presence of heart failure, alcohol consumption, patients with severely impaired renal function, neoplastic disease and chronic liver disease. Informed consent was obtained in accordance with the study protocol approved by the local ethical committee.

Coronary Angiography and Gensini Score:

Coronary angiography was performed from the percutaneous femoral approach using standard angiographic techniques. The presence and severity of CAD was determined by clinical vessel score. All coronary angiograms were evaluated by two experienced cardiologists who were blinded to the laboratory results of the patients. The severity of the each lesion was assessed by quantitative coronary angiography. The presence and total severity of CAD was assessed according to Gensini scoring system. In this system, angiographic stenosis between 1% and 25% is scored as 1 point, 26% and 50% is scored as 2 points, between 51% and 75% is scored as 4 points, between 76% and 90% is scored as 8 points, between 91% and 99% is scored as 16 points and total occlusion is scored as 32 points. These scores are multiplied by the coefficient defined for each coronary artery and segment, and the results are then added. The presence of CAD has been defined as the Gensini score being e" 1.

Definitions of CAD Risk factors:

Analyzed risk factors of CAD including age, male sex, cigarette smoking, hyperlipidemia, diabetes, hypertension, family history of CAD and hyperuricemia. Hyperlipidemia was define as plasma total cholesterol level ≥200mg/dl, LDL-cholesterol level ≥130mg/dl, triglyceride level ≥ 150mg/dl and HDL-cholesterol level ≤40 mg/dl or being on lipid lowering drugs at the time of the study. Patients were considered to have hypertension if they had received such a diagnosis with arterial pressure of more than 140/90mmHg or were being treated with antihypertensive medications. Patients were considered to have diabetes if they were taking insulin or oral hypoglycemic agents. Patients with a lack of awareness of their past history of diabetes were define as a fasting blood glucose ≥120mg/dl. Patients with hyperuricemia were defined as serum uric acid concentration ≥7.0mg/dl or ≥420 μmol/L in men and ≥6mg/dl or ≥360 μ mol/L in women.

Biochemical Analysis:

Peripheral venous blood specimens were collected from an antecubital vein after 10 hours overnight fasting. Biochemical measurements such as total cholesterol, HDL- cholesterol, triglycerides and fasting blood (FBS) levels were completed by an auto analyzer using standard methods. Low-density lipoprotein cholesterol (LDL-cholesterol) was estimated based on the friedwald formula. The uric acid concentration was measured in μmol by an enzymatic colorimetric method using uricase and peroxidase.

Results:

Patients were allocated into two groups in terms of presence of CAD. Patients with Gensini score of 0 were classified as the group without CAD and 25 patients were included in this group. Scores ≥ 1were defined as the group with CAD and183 patients were allocated in this group.

Patients with and without CAD were similar in terms of age (53.46 ± 9.95years vs. 47.16 ±7.73years, p=0.003) and significant age difference was found between patients. Gender were statistically significant p<0.001 in case male. Smoking habit was significantly more frequent (51% vs 16% p=0.002) in with CAD group and statistically significant.

There was a statistically significant difference between the mean uric acid levels of patients with and without CAD (358.23±71.11 µmol/l vs251.32±54.92 µmol/l respectively, p<0.001. There was a statistically significant difference between ejection fraction of patients with and without CAD (54.50±9.25 vs. 63.16±6.56 respectively, p<0.001.

No significant difference was found between patients with and without CAD in term of systolic (138.93±19.51 vs 141.20±18.56mmHg) and diastolic (82.79±9.70 vs. 83.60±8.60mmHg) blood pressure. There was no significant difference between patients with and without CAD in terms of the total cholesterol, LDL-C, HDL-c and family history.

When patients were stratified into four groups according to their serum uric acid quartiles, the Gensini score was found to be significantly increased across the quartiles and a statistically significant difference was noted between the groups by one-way ANOVA (p=0.001; figure 1).

Increase in the Ginsini score and frequency of CAD were exponential after the second quartile. Detailed demographic characteristic, the

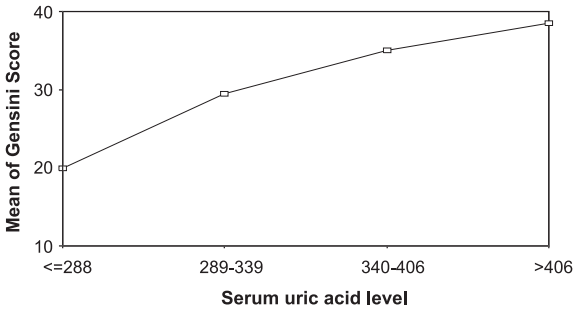

Fig.-1: *Mean Gensini score in different serum uric acid quartiles*

Table-I

Demographic features, distribution of classical risk factors, uric acid levels and distribution of Gensini scores in patients with or without CAD

Features	CAD(+), n=183	CAD(-), n=25	p-values
Age (Years)	53.46 ± 9.95	47.16 ±7.73	0.003*
Gender (male %)	90	52	<0.001*
Total cholesterol(mg/dl)	177.45±51.00	163.20±45.59	0.186
LDL-C (mg/dl)	102.05±41.62	95.64±35.60	0.464
HDL-C (mg/dl)	36.04±7.71	36.68±8.30	0.702
Uric acid(mol/l)	358.23±71.11	251.32±54.92	<0.001*
Smoking (Yes %)	51	16	0.002*
Diabetes (Yes %)	38	32	0.700
Hypertension (Yes %)	45	56	0.431
Systolic blood pressure(mmHg)	138.93±19.51	141.20±18.56	0.585
Diastolic blood pressure(mmHg)	82.79±9.70	83.60±8.60	0.691
Family history (Yes %)	37	24	0.310
Ejection fraction	54.50±9.25	63.16±6.56	<0.001*

CAD (+) = Positive (CAD present), CAD (-) = Negative (CAD absent)

distribution of cardiovascular risk factors and the Gensini scores of the groups according to uric acid quartiles are presented in Table II.

Serum uric acid level and risk factors associated with CAD (age, gender, hypertension, diadetes mellitus, smoking, HDL-C and LDL-C) were evaluated in a multivariate logistic regression analysis. Hypertension, smoking and HDL-C and increased serum uric acid level were found to be independent risk factors for the presence of CAD in all groups (for uric acid hazard ratio 1.01; 95% CI: 1.007-1.025, p< 0.001) (Table-III).

Spearman correlation analysis demonstration a positive correlation between the serum uric acid level and the severity of CAD (p=<0.001, r=0.39; Figure 1). When patients were classified into four groups according to their Gensini score, mean serum uric acid level was found to be significantly increased across the tertiles, and a statistically significant difference was detected between the tertiles (p= <0.001; figure1).

Table-II

Demographic features, distribution of classical risk factors and distribution of Gensini scores according to the serum uric acid quartiles.

Features	1st quartile ≤288 µmol/l	2nd quartile 289-339 µmol/l	3rd quartile 340-406 µmol/l	4th quartile >406 µmol/l	p-value
Age (Years)	49.82±8.46	54.55±11.84	50.29±9.96	56.52±6.81	0.001*
Gender (male %)	67	88	96	91	<0.001*
Total cholesterol(mg/dl)	180±50.47	163.39±44.56	179.60±58.20	181.43±46.31	0.202
LDL-C (mg/dl)	108.63±33.82	91.18±39.34	104.93±48.64	101.07±38.69	0.139
HDL-C (mg/dl)	36.84±9.72	35.66±7.64	35.38±7.68	36.76±5.31	0.697
Smoking (Yes %)	35	39	64	50	0.015*
Diabetes (Yes %)	37	38	38	37	0.999
Hypertension (Yes %)	45	36	60	46	0.082
Systolic blood pressure(mmHg)	137.86±18.78	137.23±19.19	144.82±18.68	136.39±20.29	0.092
Diastolic blood pressure(mmHg)	82.94±9.07	80.71±9.23	85.36±9.81	82.50±9.82	0.083
Family history (Yes %)	41	23	40	37	0.176

Table-III

Results of logistic regression analysis for several risk factors effective on the presence of CAD

Variables	β	p-value	Odds ratio	95.0% C.I.	
				Lower	Upper
Age	-0.009	0.698	0.991	0.949	1.036
Gender	0.363	0.635	1.437	0.322	6.419
Hypertension	-1.930	0.002*	0.145	0.043	0.490
Diabetes	0.964	0.155	2.623	0.695	9.907
Smoking	1.767	0.011*	5.850	1.488	23.009
HDL-C	-0.078	0.011*	0.925	0.870	0.982
LDL-C	0.003	0.639	1.003	0.989	1.018
Uric acid	0.016	0.001*	1.016	1.007	1.025

Discussion:

The main findings of this study are as follows: (i) the serum uric acid level is higher in with CAD compared with patients without CAD, (ii) the serum uric acid level is associated with the presence and severity of CAD (iii) presence and severity of CAD are higher in patients belonging to higher serum uric acid quartile group with respect to lower serum uric acid quartile group.

In our study, the mean uric acid was significantly higher in the group of the patients with coronary heart disease compared without coronary heart disease. There was a statistically significant difference between the mean uric acid levels of patients with or without CAD (358.23±71.11 mol/l vs251.32±54.92 mol/l respectively, p<0.001). Spearman correlation analysis demonstration a positive correlation between the serum uric acid level and the severity of CAD (p=<0.001, r=0.390). Logistic regression result indicates that patients of high uric level had approximately 1.01 times more chance of developing coronary heart disease than those had lower uric acid level (for uric acid hazard ratio 1.01; 95% CI: 1.007-1.025, p< 0.001) which is statistically significant.

Several epidemiological studies have identified an association between increased serum uric acid and cardiovascular risk in the general population. In the MONICA Augsburg study [18] which included a total of 1044 male patients, an increased serum uric acid level was found to be an independent risk factor for total and cardiovascular mortality. In a substudy of LIFE[19] baseline serum uric acid level was reported to be significantly associated with increased rate of the composite outcome of CV death, fatal or non-fatal myocardial infarction and or non-fatal stroke in the entire population.

In a case-control study, Hiyamuta and colleagues failed to show any relation between serum uric acid and severity of CAD in 1,029 consecutive patients undergoing coronary angiography who were divided into 4 groups according to coronary angiographic findings. In the study by two other investigarors, uric acid concentration was not independently associated with CAD or its severity.[20]

Despite several Studies investigated the relationship between uric acid and presence of CAD, very few studies have addressed the relationship between the serum uric acid level and severity of CAD. In another study, in evaluating the relationship between serum uric acid level and the severity of CAD assessed by the Gensini score, the uric acid level has been reported to be correlated with the presence, and the severity of CAD.[21]

Limitations:

Our study was observational in nature, which possibly restricted us in identifying and analyzing all potential confounding factors. Analysis are based on a single measurement of uric acid and the changes in uric acid levels over time are likely to occur. The main limitation that needs to be acknowledged regarding this study is the possible and unknown effects of the ongoing medications including diuretics on the uric acid metabolism.

Conclusion:

In conclusion, a significant association has been found between serum uric acid level and the presence and severity of CAD. In addition to the evaluation of conventional risk factors in daily clinical practice, the measurement of uric acid level might provide significant prognostic benefits in terms of global cardiovascular risk and management of the patients.

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