Association between Serum Uric Acid Level with Presence and Severity of Coronary Artery Disease

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Abstract

Aim and Objectives: This study has been undertaken to determine and compare the levels of serum uric acid in cases with and without coronary artery disease (CAD), to study association between serum uric acid (SUA) level with presence and severity of coronary artery disease.

Methods: Total 80 cases more than 13 years of age who presented to hospital with symptoms related to CAD were included in the study and divided into two groups based on coronary angiography reports. Serum uric acid level was measured in all patients by Uricase method. Presence and severity of CAD was assessed by coronary angiography. Association of SUA level with presence and severity of CAD were assessed by statistical analysis.

Results: In total, 39 (48.75%) of the patients were diagnosed with CAD having mean age of 56.71 ± 10.36 years. The CAD patients had significantly higher SUA levels than those without CAD, (7.35 ± 1.61mg/dl vs. 4.08 ± 0.83 mg/dl, p=<0.001). There was statistically significant association between SUA and severity of CAD. Serum uric acid levels were increased in cases with CAD with increase in severity of CAD ($p < 0.001$).

Conclusion: Serum uric acid was significantly associated with the presence and severity of CAD and can be used for assessing severity of CAD.

Introduction

Coronary artery disease (CAD) is most common and overwhelming cardiac disease. It is the leading cause of death in the industrialized and developing countries like India, inspite of spectacular progress in their prevention, detection and treatment over the last three decades. Coronary artery disease has rapidly emerged as the major contributor towards the increasing morbidity and mortality.[1]

Uric acid, an end product of purine metabolism, was first discovered in 1776. The role of serum uric acid in the development of cardiovascular disease has been debated for over 50 years.[2] In some studies, uric acid was found to be an independent risk factor for development of cardiovascular and cerebrovascular diseases.[3-5] The mechanism by which uric acid may play a pathogenic role in cardiovascular disease is unclear. There is strong and significant association between borderline serum uric acid levels and risk of both coronary heart disease and stroke.[6] Hyperuricemia has been associated with elevated circulating endothelin level and one of the major sites for production of uric acid in cardiovascular system is the vessel wall and particularly endothelium. Uric acid may have direct role in atherosclerotic process because atherosclerotic plaque contains more uric acid than control arteries. Hyperuricemia via purine metabolism may also promote thrombus formation.[7]

The relation between uric acid and cardiovascular disease is observed not only with frank hyperuricemia (defined as more than 5.7mg/dl in women and more than 7 mg/dl in men) but also with uric acid levels considered to be normal but at high range.[8] The present study was undertaken to determine whether raised serum uric acid levels are associated with presence and severity of CAD.

Materials and Methods

After obtaining Institutional Ethical Committee approval and written informed consent from patients, this hospital based cross-sectional study was conducted in 80 cases of either sex, having age more than 13 years and who presented to parent institute with symptoms related to CAD. All the patients were divided into two groups based on coronary angiography (CAG) reports. Patients having angiographic evidence of atherosclerosis (≥50% luminal stenosis in atleast one coronary artery or major branch segment in their epicardial coronary tree) were classified as having CAD. Patients without luminal stenosis or patients with <50% luminal stenosis were considered to have normal coronary or without CAD. Patients with conditions known to elevate uric acid level e.g. heart failure, liver disease, chronic kidney disease, gout and malignancy, patients receiving drugs affecting serum UA levels (diuretics, ethambutol, pyrazinamide, salicylates, allopurinol, probenecid) and chronic alcoholics were excluded from the study. Patients with prior history of coronary revascularisation and recent MI were excluded.

A detailed history, physical examination and all investigations including hemoglobin, CBC, renal function test, liver function test, lipid profile, ECG were done for all the patients. Serum uric acid level was measured with the Uricase method.[9-11] We included serum uric acid as continuous variable for analysis of data. All other biochemical measurements were performed as per the standard laboratory procedures at the parent institute. All the elective coronary angiographic procedures were done using GE Innova machine in parent institute. Coronary angiography was performed from the percutaneous femoral approach using standard angiographic techniques. Presence and severity of CAD was determined by clinical vessel score. All coronary

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angiograms were evaluated by experienced cardiologists who were blinded to the laboratory results of the patients. The severity of each lesion was assessed by quantitative coronary angiography. The degree of stenosis was defined as greatest percentage reduction of luminal diameter in any view compared with the nearest normal segment and was determined visually. Severity of CAD was assessed according to involvement of number of coronary vessels.

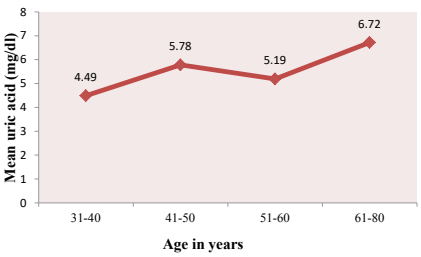

Fig. 1: Relationship of SUA with age

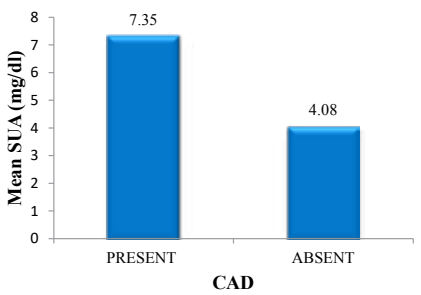

Fig. 2: Relationship of SUA with CAD

Table 1: Relationship of SUA with severity of CAD

Severity of CAD	Number	Mean SUA (mg %)
SVD	19 (48.717%)	6.71 ± 1.70
DVD	11 (28.205%)	7.33 ± 1.28
TVD	6 (15.384%)	8.5 ± 1.06
LMCA	3 (7.692%)	9.13 ± 0.05

p = < 0.001 r = 0.7157

Statistical analysis

Statistical analysis (usual descriptive and univariate analysis) was done with the help of STATA 13.0 software on a personal computer. Student t test was used to compare continuous variables and χ^2 tests were used to compare categorical variables. Unadjusted odds ratio with 95% confidence interval and p value were calculated. Multiple logistic regression analysis was performed to determine the predictors of CAD.

Observations and Results

Total 80 cases were included in the study among them 48 were males and 32 were females with male preponderance by male to female ratio of 1.5:1. The mean age of patients with CAD and without CAD was 56.71±10.36 and 48.87±9.54 years respectively. The mean serum uric acid levels were higher in males (6.21±2.17mg/dl) as compared to females (4.87±1.64mg/dl), which was statistically significant (P = 0.0040). Figure 1 shows mean serum uric acid in the various age groups which predicted that the mean uric acid increased with increase in age. Spearman's rank correlation analysis demonstrated positive correlation between age and mean uric acid, (p = 0.0100, r = 0.3394).

Total 39 cases were diagnosed with CAD, of which 31 (79.4%) were male and 8 (20.5%) were female and those without CAD were 41 of which 17 (41.5%) were male and 24 (58.5%) were female. The mean age of the cases with CAD was 56.71 ± 10.36 years. In chart mean SUA level in cases with CAD was significantly higher (7.35 ± 1.61mg/dl) than in cases without CAD (4.08 ± 0.83mg/dl), (p=<0.001). Raised serum uric acid level was associated with presence of CAD (Figure 2).

Table 1 shows mean uric acid with the severity of CAD.There was statistically significant association between SUA and severity of CAD. Serum uric acid levels were increased in cases with CAD with increase in severity of CAD.

SUA level was significantly associated with hypertension, diabetes mellitus, dyslipidemia, smoking and previous history of IHD while there was no significant association with alcohol consumption, tobacco chewing and menopause (Table 2).

Baseline characteristics were compared in patients with and without CAD; all variables except tobacco chewing and post menopausal state were associated with CAD significantly, (Table 3).

All significant variables on univariate analysis were included in Full model of multiple logistic regression analysis. After controlling potential risk factors, only smoking and uric acid were significant predictors for CAD, (Table 4).

Discussion

Despite recent advances in treatment methods, cardiovascular diseases remain as the leading cause of death in all developed countries. The well recognized risk factors like age, sex, smoking, diabetes, hypertension, dyslipidemia explain only a part of this mortality. Hence a search for other risk factors is the need of the hour. Many studies have found conflicting role of uric acid in patients with cardiovascular

Table 2: Relationship of mean uric acid with various risk factors

Risk factors		Number (%)	Mean SUA	P-value
Hypertension	Present	45 (56.25)	6.45±2.11	0.001
	Absent	35 (43.75)	4.68±1.77	
Diabetes Mellitus	Present	15 (18.75)	7.51 ± 2.43	0.0001
	Absent	65 (81.25)	5.25 ± 1.74	
Dyslipidemia	Present	17 (21.25)	6.80 ± 2.21	0.010
	Absent	63 (78.75)	5.37 ± 1.94	
Smoking	Present	17 (21.25)	6.98 ± 1.99	0.0028
	Absent	63 (78.75)	5.32 ± 1.96	
H/O IHD	Present	15 (18.75)	6.68 ± 2.42	0.0361
	Absent	65 (81.25)	5.44 ± 1.93	
Alcohol consumption	Present	19 (23.75)	6.37 ± 2.35	0.0949
	Absent	61 (76.25)	5.46 ± 1.95	
Tobacco chewing	Present	14 (17.5)	6.36 ± 1.55	0.1752
	Absent	66 (82.5)	5.53 ± 2.15	
Menopause	Present	14 (43.75)	5.48 ± 1.86	0.0621
	Absent	18 (56.25)	4.4 ± 1.32	

Table 3: Comparison of various risk factors in patients with and without CAD

Risk factors	With CAD	Without CAD	P value
Mean age (Years)	56.71±10.36	48.87±9.54	0.0011,HS
Sex			
Male	31 (79.4%)	17 (41.5%)	0.001,HS
Female	8 (20.5%)	24 (58.55%)	
Hypertension	30 (66.66%)	15 (33.33%)	<0.001,HS
Diabetes Mellitus	12 (80%)	3 (20%)	0.007, HS
Dyslipidemia	13 (76.47%)	4 (23.52%)	0.010, S
Smoking	14 (82.3%)	3 (17.7%)	0.002, HS
IHD	12 (80%)	3 (20%)	0.007, HS
Alcohol	14 (73.68%)	5 (26.31%)	0.013,S
Tobacco Chewing	9 ((64.28%)	5 (35.71%)	0.200, NS
Post Menopause	6 (42.85)	8 (57.14%)	0.627, NS
Mean SUA (mg %)	7.35±1.61	4.08±0.83	<0.0001, HS

Table 4: Multiple logistic regression analysis showing association of various risk factors with CAD

Variables	Odds Ratio	P value	[95% Conf. Interval]
Age	0.97	0.68	0.83-1.13
Gender	0.15	0.34	0.00-7.45
HTN	0.15	0.18	0.01-2.45
DM	0.1160104	0.439	0.000495-27.17661
IHD	0.01	0.12	0.00-3.21
Dyslipedimia	0.04	0.08	0.00-1.41
Smoking	68.73	0.05	1.08-4386.02
Alcohol	0.03	0.06	0.00-1.08
UA	7.63	0.00	2.04-28.48
Tobacco chewing	0.07	0.17	0.00-3.01
Post menopause	0.60	0.79	0.02-23.20

diseases. This study was conducted to assess the association of serum uric acid level with presence and severity of CAD. The main findings of the study were: (i) the serum uric acid level was higher in patients with CAD compared with patient without CAD; (ii) The serum uric acid level was associated with the presence and severity of CAD. We included serum uric acid as continuous variables. The severity of CAD was higher in patients belonging to higher serum uric acid with respect to lower serum uric acid level.

The mean age of cases with CAD was 56.71 ± 10.36 years with the range of 33 to 73 years. Majority of the cases (35%) were in the age group of 41-50 years. We observed that the serum uric acid (SUA) levels increased with increasing age. The mean SUA levels were higher among males as compared to females. These observations were statistically significant and correlated with previous studies.[12-15] The mean SUA level in cases with CAD was significantly higher (7.35 ± 1.61mg/dl) than in cases without CAD (4.08 ± 0.83mg/dl), (p=<0.001), this result was correlated with study of Deveci OS et al.[16]

Several studies have been performed to investigate the relationship between serum uric acid and different aspects of cardiovascular diseases.[6,17-19] It is well documented that uric acid is related to risk factors for CAD such as hypertension,[20-23] diabetes mellitus,[22,23] metabolic syndrome,[24] dyslipidemia,[19] and obesity.[22] 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.[25] In present study, SUA level was significantly high in patients with hypertension, diabetes mellitus, dyslipidemia while there was no significant association with alcohol consumption, tobacco chewing and menopause. On multiple logistic regression analysis, smoking was found to be independently associated with CAD and mean SUA level in smokers was significantly higher as compared to non smokers. Similarly it was observed that mean SUA level in cases with previous IHD was significantly higher as compared to those without previous IHD. These findings were in correlation with the observation found in study conducted by Nadkar *et al*[15] and Kojima *et al*.[26]

We compared baseline characteristics in patients with and without CAD; all variables except tobacco chewing and post menopausal state were associated with CAD significantly.

In current study, the mean uric acid level was significantly higher in the group of patients with CAD compared to those without CAD. Despite several studies investigated the relationship between uric acid and the presence of CAD,[3-5] very few studies have addressed the relationship between the serum uric acid level and the severity of CAD. Tuttle *et al*[27] have reported that the uric acid level was correlated with the CAD severity score in women; however, such relationship was not reported for men. 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, but not the severity of CAD.[28] Deveci OS et al[16] reported in their study that the serum uric acid level was found to be associated with presence and severity of CAD. In our study, the severity of CAD was assessed according to involvement of number of coronary vessels and study proves that there was statistically significant association between SUA and severity of CAD, (Table 1). After controlling potential conventional risk factors, only smoking and uric acid were significant predictors for CAD. Furthermore, SUA can be used for assessing severity of CAD.

Limitations of the study

It is difficult to prove the causality in cross-sectional study. So, our study cannot prove the role of uric acid as causal in the patients of CAD but it did clearly prove that SUA is associated with presence and severity of CAD.

Further long term prospective studies are needed to establish the role of SUA in CAD. Also, trial of SUA lowering drugs in ischemic heart disease patients as well as in those at increased risk of CAD can be worth considering.

Conclusion

The serum uric acid level was higher in patients with CAD compared to those without CAD. A strong 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 assessment and management of patients.

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Abbreviations

CAD: Coronary Artery Disease; SUA: Serum Uric Acid; CAG: Coronary Angiography; MI: Myocardial Infarction; ECG: Electrocardiogram; CBC: Complete Blood Count; H/O: History of; IHD: Ischemic Heart Disease.

References

1. Reddy KS. Rising burden of cardiovascular disease in India. In: Sethi KK, editor. Coronary artery disease in Indians: a global perspective. Mumbai: Cardiological Society of India. 1998; 63–72.
2. Gertler MM, Garn SM, Levine SA. Serum uric acid in relation to age and physique in health and in coronary heart disease. *Ann Internal Medicine* 1951; 34:1421-1431.
3. Niskanen LK, Laaksonen DE, Nyyssonen K et al. Uric acid level as a risk factor for cardiovascular and all-cause mortality in middleaged men: a prospective cohort study. *Arch Intern Med* 2004; 164:1546-1551.
4. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971–1992 National Health and Nutrition Examination Survey. *JAMA* 2000; 283:2404–2410.
5. Niskanen L, Laaksonen DE, Lindstrom J et al. Serum uric acid as a harbinger of metabolic outcome in subjects with impaired glucose tolerance: the Finnish Diabetes Prevention Study. *Diabetes Care* 2006; 29:709–711.

6. Bos MJ, Koudstaalet PJ, Hofman A et al. Uric acid is a risk factor for M.I. and stroke : the Rotter Dom Study. *Stroke* 2006; 37:1503-1507.
7. Zoccali C, Maio R, Mallamaci F et al. Uric Acid and endothelial dysfunction in essential hypertension. *J American Soc Nephrology* 2006; 17:1466-1471.
8. Feig DI, Kang DH, Johnson RJ. Uric acid and Cardiovascular Risk, *The New England Journal of Medicine* 2008; 359:1811-1821.
9. Fossati P, Prencipe L, Berti G. Enzymic Creatinine Assay: A New Colorimetric Method Based on Hydrogen Peroxide Measurement. *Clin Cherm* 1983; 29:1494-1496.
10. Trinder P. Determination of glucose in blood using glucose oxidase with an alternative oxygen receptor. *Ann Clin Biochem* 1969; 6:24–27.
11. International Federation of Clinical Chemistry – Clinical Chemistry Acta. 1978; 87/3: 459F.
12. Longo-Mbenza B, Luila EL, Mbete P, et al. Is hyperuricemia a risk factor of stroke and coronary heart disease among Africans? *Internat J Cardiology* 1999; 71:17–22.
13. Bickel C, Rupprecht HJ, Blankenberg S, et al. Serum uric acid as an independent predictor of mortality in patients with angiographically proven coronary artery disease. *Am J Cardiol* 2002; 89:12-17.
14. Kuzuya M, Ando F, Iguchi A, et al. Effect of aging on serum uric acid levels: longitudinal changes in a large Japanese population group. *Journal of Gerontology* 2002; 57A:M660-M664.
15. Nadkar MY, Jain VI. Serum uric acid in Acute Myocardial Infarction. *J Assoc Physicians India* 2008; 56:759-762.
16. Deveci OS, Kabakci G, Okutucu S, Tulumen E, Aksoy H, Kaya EB, Evranos B, et al. The association between serum uric acid level and coronary artery disease. *Int J Clin Pract* 2010; 64:900–907.
17. Neogi T, Ellison RC, Hunt S et al. Serum uric acid is associated with carotid plaques: the National Heart, Lung, and Blood Institute Family Heart Study. *J Rheumatol* 2009; 36:378-384.
18. Franse LV, Pahor M, Di Bari M, et al. Serum uric acid, diuretic treatment and risk of cardiovascular events in the Systolic Hypertension in the Elderly Program (SHEP). *J Hypertens* 2000; 18:1149-1154.
19. Juraschek SP, Tunstall-Pedoe H, Woodward M. Serum uric acid and the risk of mortality during 23 years follow-up in the Scottish Heart Health Extended Cohort Study. *Atherosclerosis* 2014; 233:623-629.
20. Weiss ST, Litonjua AA. Uric acid and the development of hypertension: the normative aging study. *Hypertension* 2006; 48:1031-1036.
21. Shankar A, Klein R, Klein BE, Nieto FJ. The association between serum uric acid level and long-term incidence of hypertension: Population-based cohort study. *J Hum Hypertens* 2006; 20:937-945.
22. Masuo K, Kawaguchi H, Mikami H, Ogihara T, Tuck ML. Serum uric acid and plasma norepinephrine concentrations predict subsequent weight gain and blood pressure elevation. *Hypertension* 2003; 42:474-480.
23. Nakanishi N, Okamoto M, Yoshida H, Matsuo Y, Suzuki K, Tatara K. Serum uric acid and risk for development of hypertension and impaired fasting glucose or Type II diabetes in Japanese male office workers. *Eur J Epidemiol* 2003; 18:523-530.
24. Li Q, Yang Z, Lu B et al. Serum uric acid level and its association with metabolic syndrome and carotid atherosclerosis in patients with type 2 diabetes. *Cardiovasc Diabetol* 2011; 4:72.
25. Goodarzynejad H, Anvari MS, Boroumand MA, Karimi A, Abbasi SH, Davoodi G. Hyperuricemia and the presence and severity of coronary artery disease. *Lab Med* 2010; 41:40–45.
26. Kojima S, Sakamoto T, Ishihara M, et al. Prognostic usefulness of serum uric acid after acute myocardial infarction (Japanese Acute Coronary Syndrome Study). *Am J Cardiol* 2005; 96:489-495.
27. Tuttle KR, Short RA, Johnson RJ. Sex differences in uric acid and risk factors for coronary artery disease. *Am J Cardiol* 2001; 87:1411–1414.
28. Gur M, Yilmaz R, Demirbag R et al. Relation of serum uric acid levels with the presence and severity of angiographic coronary artery disease. *Angiology* 2008; 59:166–171.