

STUDY OF SERUM URIC ACID LEVEL AS A RISK FACTOR AND FOR EVALUATING THE SEVERITY OF CORONARY ARTERY DISEASE

Shruthi S¹, Ramchandra Prabhu H. D², Tirthankar Mukherjee³

¹Assistant Professor, Department of General Medicine, Yenepoya Medical College University, Deralakatte, Mangalore.

²Associate Professor, Department of General Medicine, Kempegowda Institute of Medical Sciences and Research Centre, Bengaluru.

³Assistant Professor, Department of General Medicine, Kempegowda Institute of Medical Sciences and Research Centre, Bengaluru.

ABSTRACT

BACKGROUND

Few studies have assessed the relation of hyperuricemia 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

Fifty patients having angiographic evidence of atherosclerosis (CAD+case group) compared to 50 patients with no luminal stenosis (n=) or with <50% luminal stenosis (n=) at coronary angiography (CAD-control group).

RESULTS

The mean age of the patients was 60±10 years (317 men, 58.7%). Hyperuricemia was more likely associated with a trend toward higher vessel scores indicating a more severe CAD (adjusted OR=1.51, 95% CI=1.09-2.09; P=0.005) in the whole population.

CONCLUSION

Asymptomatic hyperuricemia was associated with the presence and severity of angiographically-defined CAD in patients with suspicious symptoms for CAD.

KEYWORDS

Uric Acid, CAD, Angiography.

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INTRODUCTION

Coronary heart disease is a worldwide health epidemic. Although, age-specific events related to CHD have fallen dramatically in the last few decades. The overall prevalence has risen as population, age and patients survive the initial coronary or cardiovascular event. Worldwide, 30 percent of all deaths can be attributed to cardiovascular disease of which more than half are caused by CHD (coronary heart disease) and the forecasts for the future estimate a growing number as a consequence of lifestyle changes in developing countries.

Globally, of those dying from cardiovascular diseases, 80 percent are in developing countries and not in the western world. Global Burden of Disease (GBD) study reported that in 1990 there were 5.2 million deaths from cardiovascular diseases in economically developed countries and 9.1 million deaths from the same causes in developing countries.¹

The prevalence of coronary artery disease in India has increased from 1 percent in 1960 to 9.7 percent in 1995 in urban populations and in rural populations it has almost doubled in the last decade.² Coronary artery disease has a

number of well-determined risk factors. The most common risk factors include smoking, family history, hypertension, obesity, diabetes, high alcohol consumption, lack of exercise, stress and hyperlipidaemia.

Hyperuricemia was postulated to be a risk factor for Coronary Artery Disease (CAD) more than 5 decades ago. Since then, numerous studies have investigated the association between elevated serum uric acid and CAD. Some studies found hyperuricemia to be an independent risk factor for CAD. We undertook this study to note the association between uric acid levels with the presence of CAD as an independent risk factor and to know relationships between uric acid levels and severity of CAD.

AIM AND OBJECTIVES

1. Study designed to determine the relationship of serum uric acid level with coronary artery disease.
2. To evaluate the risk factors of CAD including hyperuricemia to determine the independent predictors of CAD in male and female patients undergoing coronary angiography and
3. To explore whether there was a possible association between hyperuricemia and the severity of CAD in total and in men and women separately when adjusting for various confounding factors.

METHODOLOGY

The study of 100 cases with symptoms and risk factors of coronary artery disease patients undergoing coronary angiography at KIMS Hospital, Bengaluru, was conducted from September 2012 to May 2014. It was an observational prospective study for 18 months.

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Corresponding Author:

Dr. Shruthi S,

Flat No. 610, Meridian Apartments Near,

Gardenia Hostel Laxmigudda,

Nithyananda Nagar Post,

Mangalore-575018.

E-mail: shuthibhat@gmail.com

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All patients >45 years with risk factors of CAD, symptoms of CAD who were undergoing coronary angiography were included in the study.

Patients with Previous Percutaneous Transthoracic Coronary Angioplasty/stent implantation, Chronic heart failure, Gout symptoms, Chronic Alcoholic, Acute infectious and autoimmune disease, Chronic kidney disease, Neoplastic disease, Patients on Salicylates, diuretics (>2 gm), ethambutol, pyrazinamide were excluded from the study.

Patients having angiographic evidence of atherosclerosis (≥50 percent luminal stenosis in at least 1 coronary artery or major branch segment in their epicardial coronary tree) were classified as having CAD (CAD+case group). Patients without luminal stenosis at coronary angiography were considered to have normal coronary and classified as not having CAD (CAD-control group).

Coronary angiography was performed from the percutaneous femoral approach using standard angiographic techniques. The presence and severity of CAD was determined by vessel score. The angiograms were classified as revealing either no coronary lesions (absent), no coronary lesions with more than 50 percent luminal stenosis (minimal) or as having one (mild), two (moderate) or three (severe) major epicardial coronary arteries with more than 50 percent luminal obstructions. Left main stem (LMS) stenosis was regarded as one vessel. Patients with <50 percent luminal stenosis were classified as having minimal CAD. If the LMS and the Left Anterior Descending (LAD) and/or Left Circumflex (LCX) arteries were affected, this was counted as two points. The degree of stenosis was defined as the greatest percentage reduction of luminal diameter in any view compared with the nearest normal segment and was determined visually.

Definitions of CAD Risk Factors

Analysed risk factors of CAD included age, male gender, cigarette smoking, hyperlipidaemia, diabetes, hypertension, family history of CAD and hyperuricemia. Patients who currently smoked any kind of tobacco or who had quit smoking less than one month prior were considered current smokers. Hyperlipidaemia was defined as plasma total cholesterol level ≥200 mg/dL, LDL-cholesterol level ≥130 mg/dL, triglyceride level ≥200 mg/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 arterial pressure was more than 140/90 mmHg or were being treated with antihypertensive medications. Patients were considered to have diabetes if they were taking insulin or oral

hypoglycaemic agents. Patients with lack of awareness of their past history of diabetes were defined as a fasting blood glucose >126 mg/dL. A positive family history was defined as CAD in a parent or sibling noted under the age of 55 for men and 65 for women. Patients with hyperuricemia were defined as serum uric acid concentrations ≥7.0 mg/dL in men and ≥6.0 mg/dL in women.

DATA ANALYSIS

The following Methods of Statistical Analysis have been used in this study.

1. The results for each parameter (numbers and percentages) for discrete data and averaged mean+standard deviation for continuous data are presented by student test.
2. The proportion was compared using chi-square test of significance.

In all the above tests, the P values were less than 0.05, hence taken to be statistically significant. The data was analysed using Statistical Package for Social Science (SPSS, V 10.5).

RESULTS

Among these 100 patients, whom the inclusion and exclusion criteria were included in the study, 57 were males and 43 were females. 50 patients were included under CAD + group, 50 patients under CAD - group. In CAD + group, 29 were males and 21 females. In CAD - group, 28 males and 22 females. Mean age of patients was 60.1±9.387 years.

Total 49 patients had hypertension out of which 29 (50.9%) were male and 20 (46.5%) were female. 59 patients had type 2 diabetes mellitus in which 35 (61.4%) were male and 24 (55.8%) females. Among 100 patients, 19 had family history of coronary artery disease with 12 (21.1%) being males and 7 (16.3%) being females. The men had a greater prevalence of hypertension, diabetes mellitus and hyperlipidaemia compared to women. Serum levels of creatinine and uric acid were significantly greater for men than women. Among 50 CAD patients, 7 had minimal, 9 had mild, 14 had moderate and 20 had severe coronary artery disease. Out of the above 50, 29 male patients had CAD with 5 (8.8%), 5 (8.8%), 9 (15.8%) and 20 (17.5%) having minimal, mild, moderate and severe CAD respectively and 21 female patients had CAD with 2 (4.7%), 2 (9.3%), 5 (11.6%), 10 (23.3%) having minimal, mild, moderate and severe CAD respectively.

	Male (N=57)	Female (N=43)	Total (N=100)	'p' value
Age	60.2±9.625	60±9.174	60.1±9.387	0.924
Smoking	37 (64.9%)	0 (0.0%)	37 (37.0%)	<0.001
Diabetes	35 (61.4%)	24 (55.8%)	59 (59.0%)	0.574
Hypertension	29 (50.9%)	20 (46.5%)	49 (49.0%)	0.665
Family History of CAD	12 (21.1%)	7 (16.3%)	19 (19.0%)	0.547
Severity of CAD				0.857
Absent	28 (49.1%)	22 (51.2%)	50 (50.0%)	
Min.	5 (8.8%)	2 (4.7%)	7 (7.0%)	
Mild	5 (8.8%)	4 (9.3%)	9 (9.0%)	
Moderate	9 (15.8%)	5 (11.6%)	14 (14.0%)	
Severe	10 (17.5%)	10 (23.3%)	20 (20.0%)	
Hyperlipidaemia	25 (43.9%)	21 (48.8%)	46 (46.0%)	0.621
Hyperuricemia	29 (50.9%)	24 (55.8%)	53 (53.0%)	0.624

BMI	24.1±1.9951	24.8±2.6978	24.4±2.3359	0.145
Pulse	83.44±12.493	83.98±12.005	83.67±12.227	0.829
Systolic Blood pressure	133.79±17.52	127.63±10.395	131.14±15.128	0.043
Diastolic blood pressure	79.58±9.333	81.49±8.598	80.4±9.03	0.297
S. Creatinine	1.03±0.277	0.92±0.231	0.98±0.263	0.038
Uric acid (mg/dL)	5.99±1.972	5.5±1.744	5.78±1.884	0.203
Fasting blood glucose (mg/dL)	116.35±58.018	110.05±38.623	113.64±50.465	0.539
Triglyceride (mg/dL)	177.35±55.153	166.6±40.63	172.73±49.493	0.285
HDL-cholesterol (mg/dL)	35.72±3.478	36.14±3.299	35.9±3.392	0.542
LDL-cholesterol (mg/dL)	119.37±32.429	114.93±24.967	117.46±29.397	0.458
Total cholesterol (mg/dL)	195.53±37.144	193.79±33.517	194.78±35.465	0.810

Table I: The Baseline Characteristics of the Study Population

Source: Compiled from primary data.

	CAD - (N=50)	CAD + (N=50)	Total (N=100)	'p' value
Age	60.9±8.87	59.3±9.902	60.1±9.387	0.397
Gender				0.840
Male	28 (56.0%)	29 (58.0%)	57 (57.0%)	
Female	22 (44.0%)	21 (42.0%)	43 (43.0%)	
Chest Pain	38 (76.0%)	45 (90.0%)	83 (83.0%)	0.062
Breathlessness	9 (18.0%)	14 (28.0%)	23 (23.0%)	0.235
Palpitations	6 (12.0%)	3 (6.0%)	9 (9.0%)	0.295
Giddiness, Sweating	0 (0.0%)	5 (10.0%)	5 (5.0%)	0.022
Smoking	12 (24.0%)	25 (50.0%)	37 (37.0%)	0.007
Diabetes	27 (54.0%)	32 (64.0%)	59 (59.0%)	0.309
Hypertension	21 (42.0%)	28 (56.0%)	49 (49.0%)	0.161
Family history of CAD	6 (12.0%)	13 (26.0%)	19 (19.0%)	0.074
Hyperlipidaemia	5 (10.0%)	41 (82.0%)	46 (46.0%)	<0.001
Hyperuricemia	3 (6.0%)	50 (100.0%)	53 (53.0%)	<0.001
Severity of CAD				<0.001
Absent	50 (100.0%)	0 (0.0%)	50 (50.0%)	
Min.	0 (0.0%)	7 (14.0%)	7 (7.0%)	
Mild	0 (0.0%)	9 (18.0%)	9 (9.0%)	
Moderate	0 (0.0%)	14 (28.0%)	14 (14.0%)	
Severe	0 (0.0%)	20 (40.0%)	20 (20.0%)	
BMI	23.3±1.4463	25.5±2.564	24.4±2.3359	<0.001
Uric acid (mg/dL)	4.094±0.993	7.46±0.636	5.777±1.884	<0.001
Fasting blood glucose (mg/dL)	88.08±20.195	139.2±58.347	113.64±50.465	<0.001
Triglyceride (mg/dL)	144.06±9.629	201.4±56.381	172.73±49.493	<0.001
HDL-cholesterol (mg/dL)	35.58±2.749	36.22±3.935	35.9±3.392	0.348
LDL-cholesterol (mg/dL)	96.68±9.43	138.24±27.854	117.46±29.397	<0.001
Total cholesterol (mg/dL)	184.8±31.558	204.76±36.633	194.78±35.465	0.004

Table II: Baseline Characteristics of CAD + and CAD - Group

Source: Compiled from primary data

According to the above Table II, hyperlipidaemia, hyperuricemia were seen in CAD+group, which was statistically significant (<0.001). On coronary angiography, 50 percent had normal coronary arteries and 14 percent had minimal CAD. Mild, moderate, severe seen in 18, 28 and 40 percent of the patients, respectively. Mean levels of serum

uric acid were significantly higher in CAD patients than in those without CAD in total. The baseline characteristics of the participants with and without CAD in total and in men and women individually are presented in Table IIIA and IIIB.

Mean levels of FBS, TG, LDL cholesterol level and total cholesterol level were more in CAD+ group than CAD.

	Male (N=57)		'p' value
	CAD - (N=28)	CAD + (N=29)	
Age (Yrs.)	60.6±9.708	59.7±9.695	0.733
Chest Pain	20 (71.4%)	27 (93.1%)	0.031
Breathlessness	6 (21.4%)	11 (37.9%)	0.173
Palpitations	5 (17.9%)	2 (6.9%)	0.208
Giddiness, Sweating	0 (0.0%)	3 (10.3%)	0.080
Smoking	12 (42.9%)	25 (86.2%)	0.001
Diabetes	16 (57.1%)	19 (65.5%)	0.516

Hypertension	12 (42.9%)	17 (58.6%)	0.234
Family History of CAD	5 (17.9%)	7 (24.1%)	0.561
Hyperlipidaemia	1 (3.6%)	24 (82.8%)	<0.001
Hyperuricemia	0 (0.0%)	29 (100.0%)	<0.001
BMI	23.3±1.6069	24.8±2.0577	0.002
Uric acid (mg/dL)	4.15±0.922	7.76±0.579	<0.001
Fasting blood glucose (mg/dL)	86.5±18.664	145.2±68.153	<0.001
Triglyceride (mg/dL)	144.18±9.246	209.38±61.954	<0.001
HDL-cholesterol (mg/dL)	35.04±2.925	36.38±3.877	0.146
LDL-cholesterol (mg/dL)	95.36±4.931	142.55±30.767	<0.001
Total Cholesterol (mg/dL)	182.36±24	208.24±43.163	0.007

Table IIIA: Comparison of Risk Factors Among Male Patients With and Without CAD

Source: Compiled from primary data

	Female (N=43)		'p' value
	CAD - (N=22)	CAD + (N=21)	
Age (yrs.)	61.2±7.886	58.7±10.389	0.367
Chest Pain	18 (81.8%)	18 (85.7%)	0.729
Breathlessness	3 (13.6%)	3 (14.3%)	0.925
Palpitations	1 (4.5%)	1 (4.8%)	0.973
Giddiness, Sweating	0 (0.0%)	2 (9.5%)	0.138
Smoking	0 (0.0%)	0 (0.0%)	-
Diabetes	11 (50.0%)	13 (61.9%)	0.432
Hypertension	9 (40.9%)	11 (52.4%)	0.451
Family history of CAD	1 (4.5%)	6 (28.6%)	0.033
Hyperlipidaemia	4 (18.2%)	17 (81.0%)	<0.001
Hyperuricemia	3 (14.3%)	21 (100.0%)	<0.001
BMI	23.3±1.2492	26.3±2.9857	<0.001
Uric acid (mg/dL)	4.023±1.094	7.048±0.463	<0.001
Fasting blood glucose (mg/dL)	90.09±22.275	130.95±41.408	<0.001
Triglyceride (mg/dL)	143.91±10.314	190.38±46.848	<0.001
HDL-cholesterol (mg/dL)	36.27±2.394	36.0±4.099	0.790
LDL-cholesterol (mg/dL)	98.36±13.073	132.29±22.614	<0.001
Total cholesterol (mg/dL)	187.91±39.562	199.95±25.254	0.243

Table IIIB: Comparison of Risk Factors Among Female Patients With and Without CAD

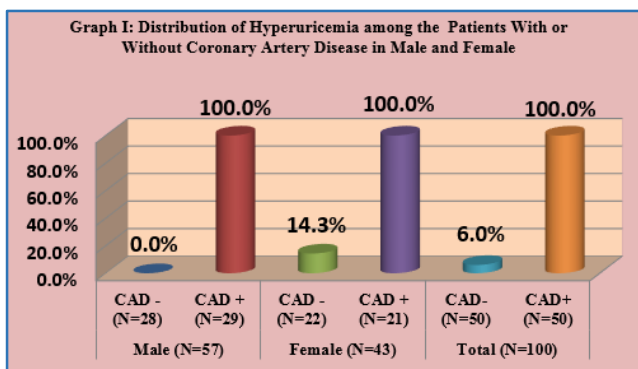
Source: Compiled from primary data.

In CAD+group, 93 percent of patients had chest pain, 28 percent breathlessness, 6 percent palpitations and 10 percent had associated other symptoms. Among male patients, 27 (93.1%), 11 (37.9%), 2 (6.9%), 3 (10.3%) had chest pain, breathlessness, palpitations and had associated with other symptoms, respectively. Among females in CAD+group, 18 (85.7%), 3 (14.3%), 1 (4.8%), 2 (9.5%) had above symptoms respectively. In CAD-group, 45 (90%) patients had chest pain, 14 (28%) had breathlessness, 3 (6%) palpitation and 5 (10%) other symptoms.

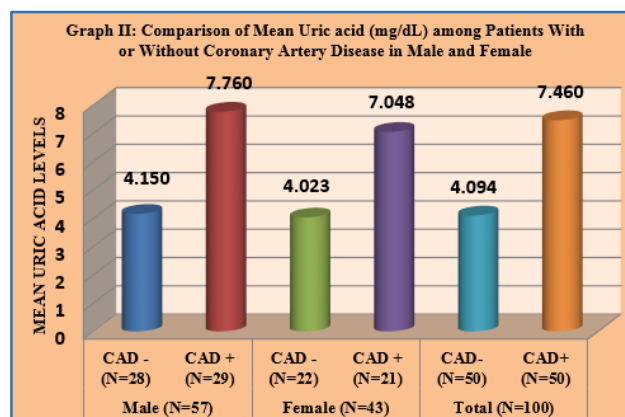
Only 3 (14.3%) in CAD-group had hyperuricemia who were all females, which was statistically significant as shown in the above Tables II, IIIA and B and Graph I, both males and females.

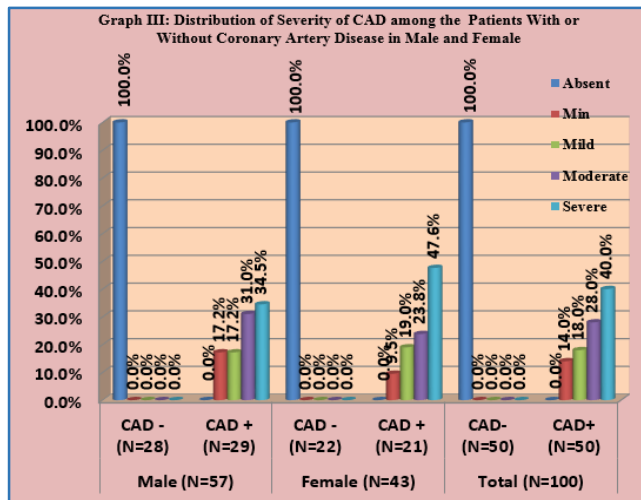
In CAD+group, mean uric acid level was 7.46±0.636 mg% with males having 7.76±0.579 mg% and females having 7.048±0.463 mg%, which was statistically significant as shown in Table IIIA (p value <0.001).

In CAD-group, mean uric acid level was 4.094±0.993 mg% with males having 4.15±0.922 mg% and Females having 4.023±1.094 mg% was statistically significant as shown in the Table IIIB (p value<0.001).



50 (100.0%) patients had hyperuricemia in CAD+group and 3 (6.0%) in CAD-group. 29 (100%) and 21 (100.0%) were females in CAD+group.





Among males in CAD positive group, 5 (17.2%), 5 (17.2%), 9 (31%), 10 (34.5%) had minimal, mild, moderate and severe CAD, which was statistically significant as shown in Table VI and Graph III.

Among females in CAD positive group, 2 (9.5%), 4 (19%), 5 (23.8%), 10 (47.6%) had minimal, mild, moderate and severe CAD, which was statistically significant as shown in Table VI above and Graph III.

	Absent	Minimal	Mild	Moderate	Severe	'p' value
All	n=50	n=7	n=9	n=14	n=20	
Uric acid (mg/dL)	4.09±0.993	7.09±0.219	7.32±0.626	7.40±0.485	7.70±0.763	<0.001
Hyperuricemia	3 (6.0%)	7 (100.0%)	9 (100.0%)	14 (100.0%)	20 (100.0%)	<0.001
Male	n=28	n=5	n=5	n=9	n=10	
Uric acid (mg/dL)	4.15±0.922	7.12±0.217	7.60±0.235	7.60±0.502	8.30±0.427	<0.001
Hyperuricemia	0 (0.0%)	5 (100.0%)	5 (100.0%)	9 (100.0%)	10 (100.0%)	<0.001
Female	22	2	4	5	10	
Uric acid (mg/dL)	4.02±1.094	7.00±0.283	6.98±0.826	7.04±0.089	7.09±0.482	<0.001
Hyperuricemia	3 (13.6%)	2 (100.0%)	4 (100.0%)	5 (100.0%)	10 (100.0%)	<0.001

Table IV: Relation of SUA and Severity of CAD Among Male and Female Patients With and Without CAD

Source: Compiled from primary data.

Mean uric acid level in all patients according to severity of CAD was found to be 7.09±0.219 mg% in minimal, 7.32±0.626 mg% in mild, 7.40±0.485 mg% in moderate, 7.70±0.763 mg% in severe category respectively, which was statistically significant (p value <0.001) as shown in the above Table VI.

Mean uric acid level in male patients according to severity of CAD was found to be 7.12±0.217 mg%, 7.60±0.235 mg%, 7.60±0.502 mg%, 8.30±0.427 mg% in minimal, mild, moderate, severe category of CAD, respectively. This is statistically significant as shown in above Table VI.

Mean uric acid level in female patients according to severity of CAD was found to be 7.00±0.283 mg%, 6.98±0.826 mg%, 7.04±0.089 mg%, 7.09±0.482 mg% in minimal, mild, moderate, severe form of CAD.

DISCUSSION

In our study of investigating 100 patients undergoing coronary angiography, we found that hyperuricemia was associated with the presence of angiographically documented CAD in the whole population in men and women individually, and that this association was independent of other confounding cardiovascular risk factors. Moreover, we found that patients with hyperuricemia showed independently a trend to more severe CAD scaled by vessel score.

Fang and colleagues in the NHANES I epidemiologic followup study on a representative sample of the United States adult population showed that increased levels of serum uric acid are related to increased cardiovascular morbidity and mortality.³ Madsen and colleagues suggested that in patients with significant CAD (stenosis ≥70% in coronary angiography), high levels of serum uric acid could be a strong risk factor for adverse outcome and mortality.⁴

Our findings add to the growing body of evidence that hyperuricemia is independently associated with the development of CAD. Despite this, because of complex interrelationships of uric acid levels with many other established cardiovascular risk factors such as metabolic syndrome, obesity, diabetes and chronic renal disease.^{5,6,7}

In a Tuttle and colleagues study, there was also a linear correlation between uric acid levels and CAD severity in women, but not in men.⁸ Recently, Jelic-Ivanovic and colleagues compared the levels of uric acid in 356 patients with significant coronary lesion (≥50%) as a case group with 350 people in a control group (coronary luminal narrowing <50%). After adjusting for confounders, they found differences between the uric acid concentrations in the case vs. control group only in women; no significant differences were observed in men with or without significant coronary lesions in their study.⁹

Persky et al studied, the association between uric acid and the prevalence of ECG abnormalities and with mortality appear to be secondary to associations between uric acid and other risk factors in men.¹⁰ Gur M, Yilmaz R, Demirbag R et al studied relation of serum uric acid levels with the presence of angiographic coronary artery disease.¹¹ Some studies have found association of serum uric acid with ischaemic heart disease and hypertension.¹²

Li Qin†, Zhen Yang †, Hongxia Gu, Shuai Luet et al studied association between serum uric acid levels and cardiovascular disease in middle-aged and elderly Chinese individuals and concluded that elevated serum uric acid level was associated with cardiovascular disease, independent of conventional cardiovascular disease risk factors and metabolic syndrome.¹³

In our study, the independent adjusted association of hyperuricemia with the severity of CAD was investigated in patients having normal coronary arteries, minimal CAD, 1-vessel, 2-vessel and 3-vessel disease. In our study, patients with smoking history, elevated BMI, hyperlipidaemia with elevated triglyceride, LDL, total cholesterol, elevated fasting blood sugar levels, hyperuricemia was associated with CAD + group.

CONCLUSION

Our total hyperuricemia study population was independently associated with angiographically documented CAD. Additionally, in multiple regressions, CAD severity in all and in men and women was independently related to hyperuricemia. Our findings suggest that asymptomatic hyperuricemia has an independent role in cardiovascular disease. Asymptomatic hyperuricemia was associated with the presence and severity of angiographically-defined CAD in patients with suspicious symptoms for CAD.

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