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Original Research Article.

Role of Serum Uric Acid Level as a Probable Indicator for Severity of Coronary Artery Disease: An Observational Study

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ABSTRACT

Background: Hyperuricemia often accompanies metabolic syndrome, hypertension, diabetes, dyslipidemia, chronic renal disease, and obesity, and the serum uric acid level is known to vary significantly depending on meals, lifestyle, gender, and previous use of diuretics. Few studies have assessed the relation of hyperuricemia with the severity of coronary artery disease (CAD). The aim of this study is to evaluate a number of risk factors of CAD including hyperuricemia to determine the independent predictors of CAD in male and female patients undergoing coronary angiography and 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.

Materials & Methods: A Hospital based observational analysis done on 500 patients (320 men, 64%) who, between January 2019 and January 2020, were consecutively admitted at our institution due to symptoms related to CAD.430 patients having angiographic evidence of atherosclerosis (CAD + case group) compared to 70 patients at coronary angiography (CAD – control group).

Results: Our study showed that the mean age of the patients was 62 ±10 years, and 64% were men. The overall prevalence of cardiovascular risk factors including hypertension, diabetes mellitus, cigarette smoking, hyperlipidemia, and family history of CAD were high. There was a strongly significant linear trend of higher prevalence of hyperuricemia as well as higher concentrations of uric acid with increasing numbers of diseased vessel (*P*=0.001 and *P*<0.001).

Conclusion: We concluded that asymptomatic hyperuricemia may have an independent role in cardiovascular disease, and it should not be considered biologically inert.

Keywords: CAD, Cardiovascular Risk Factors, Hyperuricemia, Hypertension.

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INTRODUCTION

Hyperuricemia was postulated to be a risk factor for coronary artery disease (CAD) more than 5 decades ago by Gertler and colleagues.[1] 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.[2-4] Hyperuricemia often accompanies metabolic syndrome, hypertension, diabetes, dyslipidemia, chronic renal disease, and obesity, and the serum uric acid level is known to vary significantly depending on meals, lifestyle, gender, and previous use of diuretics.[5] Based on these facts, it is believed that the uric acid level only partly reflects the lifestyle origins of the disease, and it merely serves as a marker of cardiovascular disease. Furthermore, since female hormones lower the serum uric acid levels, they tend to increase after menopause, and the evaluation of uric acid becomes more difficult. The number of confounding factors involved in evaluating serum uric acid levels complicates the sole analysis of uric acid; indeed, intervention tests that focused only on uric acid are rare.

In addition, some investigators have reported an independent relationship of uric acid and CAD in women but not in men. Few studies have assessed the relation of hyperuricemia with the severity of coronary artery disease (CAD). The aim of this study is to evaluate a number of risk factors of CAD including hyperuricemia to determine the independent predictors of CAD in male and female patients undergoing coronary angiography and 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.

MATERIALS & METHODS

A Hospital based observational analysis done on 500 patients (320 men, 64%) who, between January 2019 and January 2020, were consecutively admitted at our institution due to symptoms related to CAD.

Inclusion Criteria

- The study will be carried out in pt consecutively undergoing CAG at our institute admitted due to symptoms related to CAD.
- Patients having angiographic evidence of atherosclerosis (≥50% luminal stenosis in at least 1 coronary artery or major branch segment in their epicardial coronary tree) will be classified as having CAD.
- Patients without luminal stenosis or patients with <50% luminal stenosis at coronary angiography will be considered to have normal coronary

Exclusion Criteria

- Presence of heart failure
- Malignancy
- Pregnancy
- Impaired renal function (serum Cr levels >1.5 mg/dL)
- Diuretic, antioxidants, or alcohol use, as well as taking medications targeted to lower uric acid levels.

Definitions of CAD Risk Factors

- Analyzed risk factors of CAD included age, male sex, cigarette smoking, hyperlipidemia, diabetes, hypertension, family history of CAD, and hyperuricemia.
- Patients who currently smoked any kind of tobacco or who had quit smoking less than 1 month prior were considered current smokers.
- Hyperlipidemia 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 they had received such a diagnosis with arterial pressure of 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 hypoglycemic agents.
- Patients with a 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.
- Coronary angiography plan to performed from the percutaneous femoral & radial approach using standard angiographic techniques.
- The presence and severity of CAD will be determined by clinical vessel score.
- The angiograms would be classified as revealing either no coronary lesions (absent), no coronary lesions with more than 50% luminal stenosis (minimal), or as having 1 (mild), 2 (moderate), or 3 (severe) major epicardial coronary arteries with more than 50% luminal obstructions.
- Left main stem (LMS) stenosis will be regarded as 1 vessel. Patients with <50% luminal stenosis will be classified as having minimal CAD. The degree of stenosis will be defined as the greatest percentage reduction of luminal diameter in any view compared with the nearest normal segment and will be determined visually.

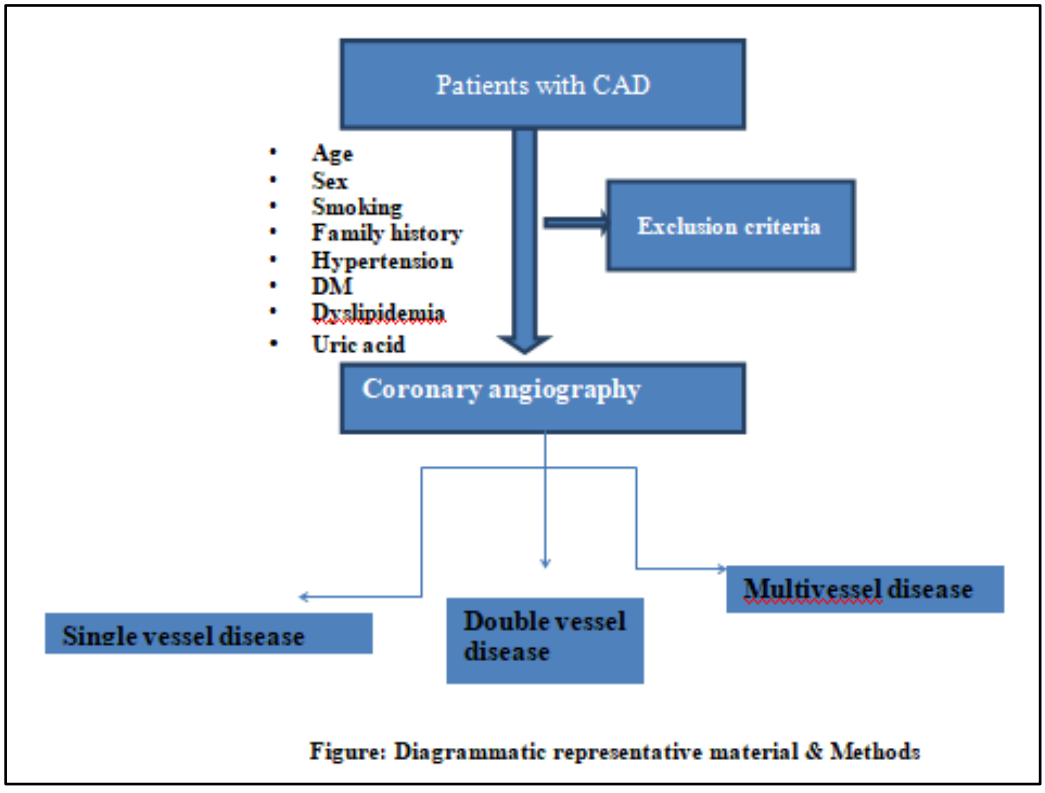


Figure: Diagrammatic representative material & Methods

Biochemical Analyses: Peripheral venous blood specimens will be collected from an antecubital vein after 10 hours of overnight fasting. Biochemical measurements such as total cholesterol, HDL-cholesterol, triglycerides, and fasting blood sugar (FBS), uric acid levels, Low-density lipoprotein cholesterol (LDL-cholesterol) will be estimated in central lab.

Statistical Analysis: Difference in mean of two group would be analysed using student's t test and Difference in proportion would be analysed using chi-square test. For the statistical analysis, the statistical software SPSS version 24.

RESULTS

Our study showed that the mean age of the patients was 62 ± 10 years, and 64% were men. The overall prevalence of cardiovascular risk factors including hypertension, diabetes mellitus, cigarette smoking, hyperlipidemia, and family history of CAD were high. The women had a greater prevalence of hypertension, diabetes mellitus, and hyperlipidemia compared to men, but cigarette smoking was much more common in men than in women. Men and women similarly showed a family history of CAD. Unsurprisingly, serum levels of creatinine and uric acid were significantly greater for men than women (table 1).

The baseline characteristics of the participants with and without CAD in total and in men and women individually are presented in Table 2. There was a strongly significant linear trend of higher prevalence of hyperuricemia as well as higher concentrations of uric acid with increasing numbers of diseased vessel (*P*=0.001 and *P*<0.001) (table 3).

Table 1: Baseline Characteristics of the Study Population

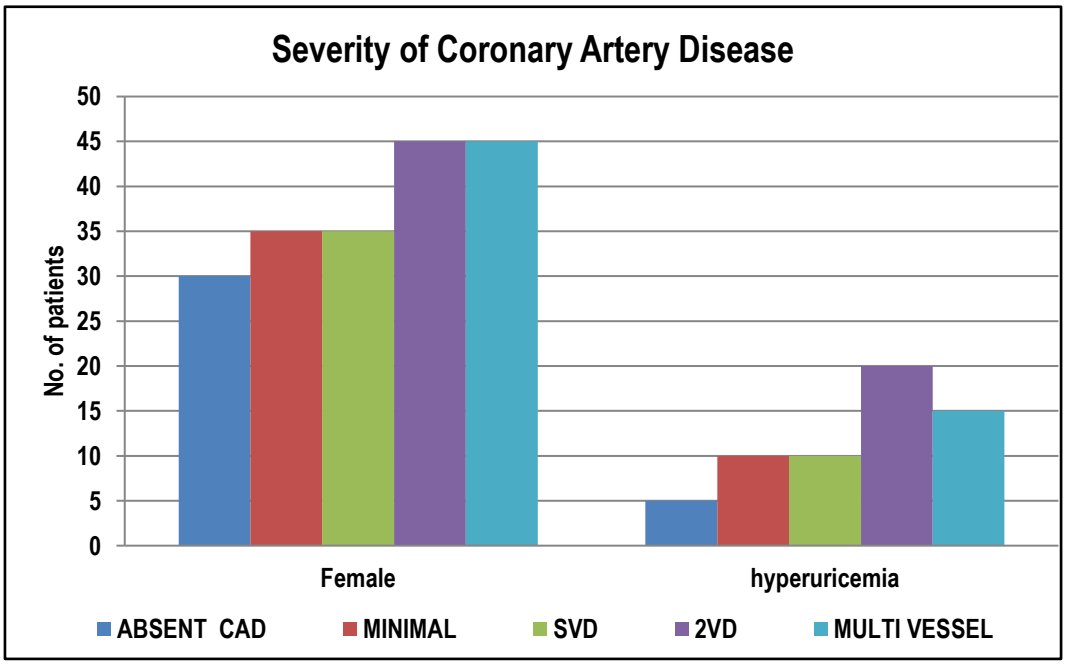
Variables	All Patients (500)	Male (320)	Female (180)	P-value
Age	62±10	61.45±9.70	62.75±8.65	>0.05
Cigarette smoking	57% (285)	72% (230)	30% (55)	1.00
Hypertension	53% (265)	56% (180)	47% (85)	<0.001
Diabetes	48% (240)	51% (165)	41% (75)	<0.001
Family history of CAD	24% (120)	25% (80)	22% (40)	>0.05
Hyperuricemia	35% (175)	35.93% (115)	33.33% (60)	>0.05
Uric acid (mg/dL)	7.27±2.22	7.62±2.08	6.77±2.32	<0.001
Hyperlipidemia	47% (235)	53.12% (170)	36.11% (65)	<0.001
Triglyceride (mg/dL)	194.28±113.72	192.38±112.25	196.99±115.98	>0.05
HDL-cholesterol (mg/dL)	40.60±10.48	38.49±9.11	43.61±11.53	<0.001
LDL-cholesterol (mg/dL)	115.64 ± 39.89	112.00 ± 37.02	120.83 ± 43.23	<0.001
Total cholesterol (mg/dL)	191.77±46.65	186.36±43.15	199.47±50.32	0.002
Creatinine (mg/dL)	1.0±0.62	1.1±0.89	0.9±0.58	<0.001

Table 2: Demographic and Clinical Characteristics of the Patients with or without Coronary Artery Disease Stratified by Sex

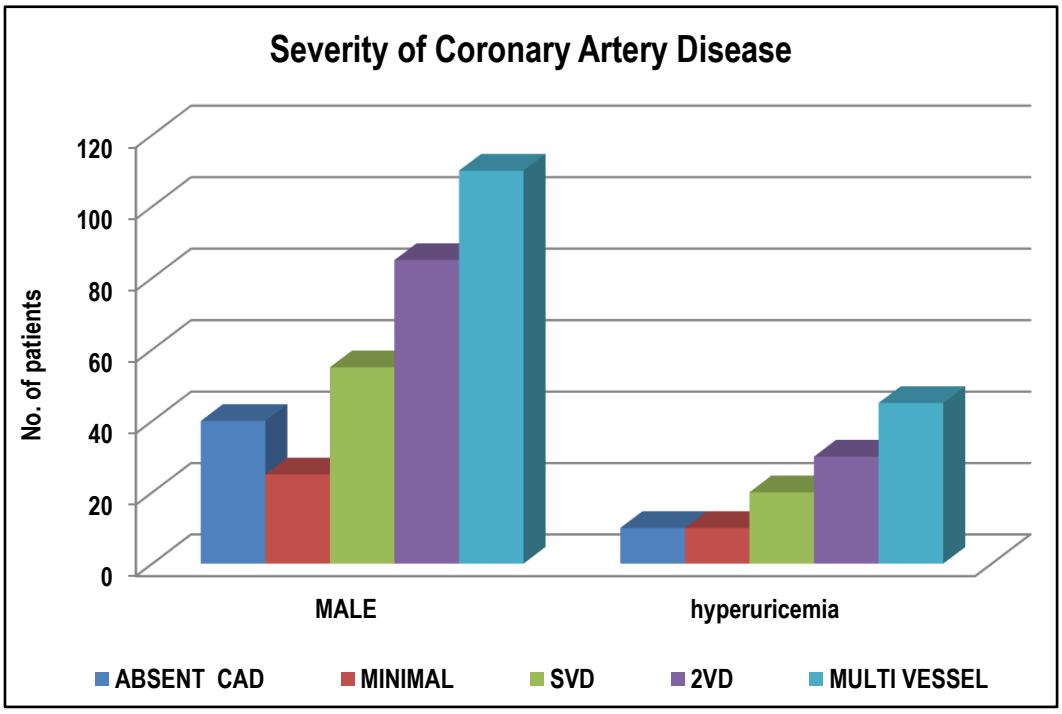
	All (500)			Male (320)			Female (180)		
	CAD+(430)	**CAD-(70)**	**P-value**	**CAD+(280)**	**CAD-(40)**	**P-value**	**CAD+(150)**	**CAD-(30)**	**p-value**
AGE	61.12±9.45	56.83±9.80	<0.01*	60.15±9.79	56.52±10.98	<0.01*	62.95±8.50	57.07±8.82	<0.01*
Cigarette smoking	61.62%(265)	28.57%(20)	<0.01*	78.57%(220)	25%(10)	<0.01*	30%(45)	33% (10)	<0.01*
Hypertension	56.97% (245)	28.57% (20)	<0.01*	58.92% (165)	37.5% (15)	<0.01*	53.33% (80)	16.66% (5)	<0.01*
Diabetes	50% (215)	35.71%(25)	<0.01*	53.57% (150)	37.5% (15)	<0.01*	43.3% (65)	33.3% (10)	<0.01*
Family history of CAD	25.58%(110)	14.2% (10)	<0.01*	26.7%(75)	12.5% (5)	<0.01*	23.3% (35)	16.66% (5)	<0.01*
Hyperuricemia	37.2%(160)	21.4%(15)	<0.01*	37.5%(105)	25%(10)	<0.01*	36.6%(55)	16.66% (5)	<0.01*
Uric acid (mg/dL)	7.55±2.27	6.66±1.97	<0.01*	7.78±2.09	7.13±1.98	>0.01	7.13±2.54	6.29±1.90	<0.01*
Hyperlipidemia	48.83%(210)	35.71% (25)	<0.01*	55.35% (155)	37.5% (15)	<0.01*	36.33% (55)	33.33% (10)	<0.01*
Total cholesterol (mg/dL)	192.25 ± 47.85	190.74 ± 44.05	>0.01	189.72 ± 43.70	175.53 ± 39.72	<0.01*	197.04 ± 54.71	202.74 ± 43.78	>0.01
HDL-cholesterol (mg/dL)	38.74 ± 9.85	44.67 ± 10.67	<0.01*	37.18 ± 8.39	42.69 ± 10.07	<0.01*	41.67 ± 11.62	46.22 ± 10.93	<0.01*
LDL-cholesterol (mg/dL)	115.84 ± 39.75	115.22 ± 40.32	>0.01	114.30 ± 36.79	104.56 ± 37.03	<0.01*	118.81 ± 44.92	123.45 ± 41.02	<0.01*
Triglyceride (mg/dL)	204.14 ± 119.70	172.83 ± 96.37	<0.01*	203.12 ± 113.24	157.72 ± 102.21	<0.01*	206.07 ± 131.49	184.76 ± 90.26	<0.01*

Table 3: Unadjusted Serum Uric Concentrations and Prevalence of Hyperuricemia in Patients with Various Severity of Coronary Artery Disease

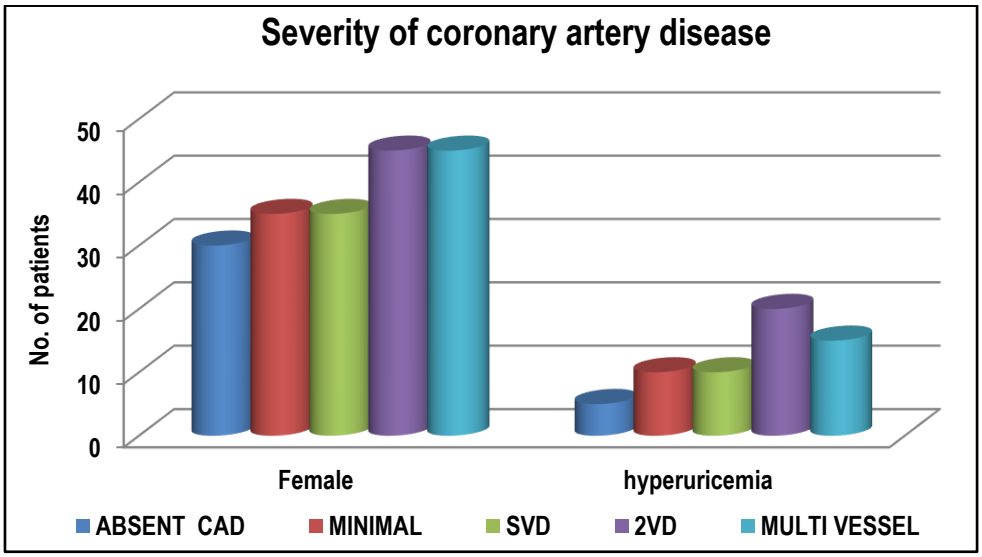
	Absent CAD	Minimal	SVD	2VD	Multi Vessel	P-value
Total Pt(500)	14%(70)	12%(60)	18%(90)	25%(125)	31%(155)	<0.01**
hyperuricemia	21.42%(15)	33.33%(20)	33.33%(30)	40%(50)	38.70%(60)	
			Male			
Male (320)	12.5%(40)	7.80%(25)	17.18%(55)	26.56%(85)	34.37%(110)	<0.05*
hyperuricemia	25%(10)	40%(10)	36.36%(20)	35.29%(30)	40.90%(45)	
			Female			
Female(180)	16.6%(30)	19.4%(35)	19.4%(35)	25%(45)	25%(45)	<0.05*
hyperuricemia	16.66%(5)	28.57%(10)	28.57%(10)	44.44%(20)	33.33%(15)	



Graph 1: Serum Uric Concentrations and Prevalence of Hyperuricemia in Patients With Various Severity of Coronary Artery Disease



Graph 2: Serum Uric Concentrations and Prevalence of Hyperuricemia in Male Patients With Various Severity of Coronary Artery Disease



Graph 3: Serum Uric Concentrations and Prevalence of Hyperuricemia in Female Patients With Various Severity of Coronary Artery Disease

DISCUSSION

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,[6,7] it is still unknown whether high serum uric acid is causally an independent risk factor, a consequence, or merely a marker for CAD. Even though most of the studies investigated the association between uric acid levels with the presence of CAD and its risk factors, studies examining relationships between uric acid levels and severity of CAD are few.[8,9]

Although data from analysis of the Framingham Heart Study and ARIC study[10,11] showed no association between uric acid and CAD, numerous recent studies have revealed that uric acid may be associated with the presence of CAD.[12,13] Most importantly, Fang and colleagues in the NHANES I epidemiologic follow-up 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.[14] Additionally, 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.[15]

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.[8] Because only 3 of their patients with non-significant (<50%) luminal narrowing had normal coronary with no stenosis, they did not perform any statistical analyses on this group.

Such disparity in study results may be due to the fact that the serum uric acid level is significantly affected by genetic backgrounds and lifestyles,[16] varying in different regions across the world. Another explanation for differences in study findings may be due to various study populations and sample sizes.

CONCLUSION

We concluded that asymptomatic hyperuricemia may have an independent role in cardiovascular disease, and it should not be considered biologically inert. Further clinical and experimental studies are required to provide stronger evidence before any intervention is recommended.

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