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Relationship of serum uric acid level and angiographic severity of coronary artery disease in patients presenting with acute coronary syndrome

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ABSTRACT:

Background: Large epidemiologic studies have shown that hyperuricemia is associated with an increased incidence of coronary artery disease.

Aims: This study aims to explore the relationship between serum uric acid level and Gensini score, which in turn reflects the severity of coronary artery disease

Methods: A retrospective cohort study was conducted in patients presenting with ACS at tertiary care centre, Bagalkot. Hyperuricemia was defined as serum uric acid level > 6 mg/dl. Severity of coronary artery disease was assessed on the basis of Gensini score. Number of diseased vessels, critical lesions and total occlusions on coronary angiogram was taken into consideration

Results: Mean uric acid levels of normouricemic and hyperuricemic groups were 4.7±1.1 and 7.53 ± 1.32 respectively with p value of 0.001. Mean Gensini score of normouricemic group was (20.56 ± 13.66) while hyperuricemic group was (35.53 ± 17.84). Chi square, independent t test was applied to compare the Gensini score of two groups and it resulted in p valve of 0.001 which is statistically significant. Spearman correlation revealed a positive correlation between serum uric acid level and Gensini score which was found to be statistically. Significant difference was observed in total occlusions (p=0.001) and left main coronary artery stenosis s (p=0.001) which were higher in the hyperuricemic group compared to normouricemic group.

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Conclusion: Hyperuricemia is associated with higher Gensini score and more frequency of total occlusions and left main coronary artery stenosis. It is an independent factor for evaluating the degree and severity coronary artery stenosis.

Keywords: Hyperuricemia, Coronary artery disease, Gensini score, Serum uric acid

INTRODUCTION

Cardiovascular diseases (CVDs) include ischemic heart disease and cerebrovascular accidents (stroke) are the primary cause of 17.7 million deaths worldwide.(1) It is well known that Indians have the highest rates of coronary artery disease (CAD), and that this elevated risk is not explained by the traditional risk factors. Acute coronary syndrome and ST-elevation myocardial infarction (MI) are currently most common in India.(2)It was projected that 244.11 million individuals worldwide have IHD in 2020. In 2020, it is anticipated that 8.95 million fatalities were related to IHD.(3) Age-standardized mortality rates from cardiovascular illnesses are rising, with 248.6 to 350.9 deaths per 100,000 people in South Asia (including India) in 2021.(4)Not only do Indians have a higher rate of CVD, but they also have a tendency to develop the disease at a younger age and have more severe and extensive disease.(5) Almost 90% of the acute myocardial infarctions could be explained by the nine conventional and non-conventional risk factors such as dyslipidemia, smoking, hypertension, diabetes mellitus , abdominal obesity, psychosocial factors, lack of regular physical activity, consumption of alcohol, and lower intake of fruits and vegetables.(6)

The complex condition known as acute coronary syndromes (ACS) can be brought on by inflammation, plaque rupture and subsequent thrombosis, gradual mechanical blockage, and dynamic obstruction.(7) The endothelium is directly implicated in the development of atherosclerosis and plays a crucial role in the regulation of vascular tone, platelet activity, leukocyte adhesion, and thrombosis. It has been noted that patients with established coronary artery disease exhibit endothelial dysfunction. (8) An rising body of research indicates that a substantial amount of endothelial dysfunction is caused by elevated oxidative stress.(9) In experimental models of atherosclerosis, there is a correlation between decreased endothelial vasomotor function and elevated production of free radicals originating from oxygen, such as superoxide anion.(10)

The final byproduct of purine metabolism is uric acid. Uric acid is produced from its direct precursor, xanthine, by an enzyme known as xanthine oxidoreductase.(11) Numerous oxygen free radicals are produced by uric acid (12,13), and these radicals take part in a cascade of inflammatory events and damage the endothelium-mediated vasodilation function, ultimately resulting in vascular endothelial dysfunction.(14) Furthermore, uric acid triggers

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the coagulation system, generates a range of cytokines, and exacerbates platelet adhesion and aggregation, all of which increase the risk of thrombosis.(15) Uric acid can disrupt nitric oxide production, reduce nitric oxide's bioavailability, trigger the renin-angiotensin system, encourage the growth of vascular smooth muscle cells and platelet aggregation, and ultimately result in endothelial dysfunction.(16) These pathways provide a solid theoretical foundation for the predictive utility of blood uric acid in determining the severity of coronary heart disease, in addition to explaining how hyperuricemia influences and promotes the onset and progression of atherosclerosis.(17)

Therefore, measuring blood uric acid will make it easier to assess the severity of ACS, categorize lesions, schedule interventions appropriately, foresee problems after MI, and give at-risk patients prompt preventive therapy. The type of interventional therapy plan used for coronary artery lesions depends on the morphology and degree of stenosis. Pharmacotherapy may be used in the future to lower uric acid levels, which may lessen the severity of CAD and, ultimately, lower the disease's death and morbidity rates.

MATERIALS AND METHODS

Study participants

A total of 110 patients who underwent coronary angiography due to suspected coronary heart disease in the Cardiac Catheterization Laboratory of a tertiary care centre at Bagalkot from March 2023 to March 2024 were selected as the research subjects. ACS patients with NSTEMI, STEMI and unstable angina who underwent angiography or percutaneous coronary intervention, who were willing and consented for the study, were included. Patients with past history of IHD, liver and kidney diseases, haematological or oncological disorders, and secondary causes of hyperuricemia were excluded from the study. Hyperuricemia was defined as serum uric acid levels > 6 mg/dl.

Sample size calculation: Sample size estimation was done using OpenEPi Software Version 2.3.1.At 95% confidence level, and 80% power of the study

α (two-tailed) =0.050 and at 95% confidence level.

β = 0.200 and 80% of power of the study

Where $Z\alpha$= standard table value for 95% CI =1.96

$Z_{1-\beta}$ = Standard table value for 80% Power = 0.84

Based on previous study:

Mean±SD of Gensini score in exposed cohort (Hyperuricemia with CAD) was found to be 35.68±26.80

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Mean±SD of Gensini score in unexposed cohort (Normouricemia with CAD) was found to be 22.15±21.52

Sample size is calculated using the formula,

$n= 2(Z\alpha+ Z_{1-\beta})^2 \sigma^2 / d^2$

sample size estimated is 51=55 in each group.

55 hyperuricemia with cad

55 normouricemia with cad

Data collection

A well-structured questionnaire was used to obtain the following data : demographic characteristics; history of hypertension, diabetes, dyslipidemia, family history of ischemic heart disease, tobacco chewing, alcoholism; heart rate, systolic blood pressure (SBP) and diastolic blood pressure measured during hospitalisation; laboratory parameters such as serum uric acid, (total cholesterol, triglycerides, low- density lipoprotein cholesterol (LDL-C), high- density lipoprotein cholesterol (HDL- C), and troponin I (TnI); echocardiography results; coronary angiography results during hospitalisation were recorded.

Assessment of coronary stenosis

An accepted angiographic scoring system to measure the severity of CAD is the Gensini score. It was created to describe the complexity of CAD. It takes into account the severity score, the regional multiplication factor, and the collateral regulation factor for every coronary artery lesion. The product of the lesion's location and stenosis degree yields the Gensini score.(18)

In terms of critical lesions and total occlusions, coronary artery lesions are more sever e the higher the Gensini score. It is a fairly scientific evaluation method that considers the number, location, and severity of coronary artery lesions.The coronary artery is divided into 1 4 parts by the scoring method, and each segment has a unique weighted coefficient.

The principal arteries supplying the left ventricle are, in particular, the left main artery and the proximal and middle segments of the left anterior descending branch; so, their weighting coefficient is larger. The Gensini score is currently able to assess the severity of coronary artery lesions in conjunction with specific biochemical markers and predict the risk of major adverse cardiovascular and cerebrovascular events (MACCEs) (19) in patients with various forms of CAD, according to a number of studies. (20,21) A critical lesion was defined as 50% or more of left main stem stenosis or ≥70% of stenosis involving the proximal portion of any of the three main coronary arteries. The definition of total occlusion was 100% occlusion without any antegrade contrast flow distal to the lesion.

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Table 1: Gensini number assigned according to degree of luminal narrowing

Luminal Narrowing (%)	Grading of disease	Gensini number
30-50	Mild	01
51-70	Moderate	02
71-90	Severe	04
91-99	Subtotal occlusion	08
100	Total occlusion	16

Table 2: Gensini multiplying factor assigned according to the location of lesion in the coronary tree

Location of lesion	Multiplying factor
Left main stem	05
Proximal LAD and proximal LCX	2.5
Mid LAD	1.5
Distal LAD, first diagonal, mid LCX, distal LCX, obtuse marginal, proximal RCA, mid RCA, distal RCA,PDA	1.0
Second diagonal, PLV	0.5

STATISTICAL ANALYSIS

Data collected was entered in MS Excel and analysis was carried out using statistical software called SPSS version 20. The results were expressed in the form of descriptive statistics like mean, standard deviation, frequency and graphs. Inferential statistics like spearman corelation, independent t test, chi square was used. If $p<0.05$ the data was considered as statistically significant.

Ethical consideration: Study was presented before the Institutional Ethical Committee and was approved

Funding: Research was funded by the participant

RESULTS

The study population included 110 patients of ACS, out of which 55 had hyperuricemia and 55 had normouricemia. Mean uric acid levels of normouricemic and hyperuricemic groups were 4.7 ± 1.1 and 7.53 ± 1.32 respectively with p value of 0.001 .The

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Mean age group of normouricemic group was (57.02 ± 11.16 years), hyperuricemic group was (60.91 ± 10.29years), p value being 0.074. Diabetics in normouricemic group were 23% and 61% in hyperuricemic group, p value was 0.036. Hypertensives constituted 55% in normouricemia group, while there were 45% in hyperuricemic group, p value being 0.036. 33.3% patients in normouricemic group had dyslipidemia as compared to 66.7% patients in hyperuricemic group (P= 0.036). Family history of IHD was present in 31.6% patients in normouricemic group as compared to 68.4% of patients in hyperuricemic group. (p=0.077). Patients consuming tobacco were 30.9 % in normouricemia group as compared to 25.5 % patients in hyperuricemic group (p= 0.03). Alcoholics constituted 1.8% in normouricemic group, while 10.9 % in hyperuricemic group (p=0.02).

Mean Gensini score of normouricemic group (24.78 ± 13.64) while hyperuricemic group was (33.94 ± 17.68). Mann Whitney U test was applied to compare the Gensini score of 2 groups and it resulted in p valve of 0.04 which shows statistically significant difference between 2 groups. Direct correlation between serum uric acid levels and Gensini score was also found to be statistically significant using Spearman correlation. Greater number of chronic total occlusions were observed in hyperuricemic group which accounted to 32.7% (P=0.001) while it was 14.5%in normouricemic group. Left main coronary artery stenosis was higher (16.4%) in hyperuricemic group while normouricemic group showed no stenosis (p=0.001). Critical lesions constituted 70 %in the normouricemic group and 80% in the hyperuricemic group (p=0.267).

Figure 1: Pie chart

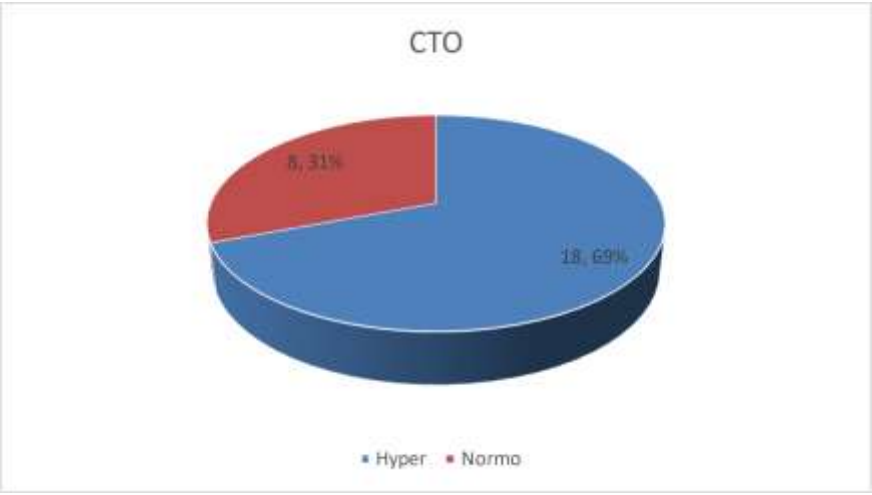

Table 1: Comparison of various parameters among study groups

Parameter	Hyperuricemia (55)	Normouricemia (55)	P-value
Mean Uric acid level	7.53 ± 1.32	4.7 ± 1.1	**0.001**

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Age	60.91 ± 10.29	57.02 ± 11.16	0.074
Sex **a. Male** **b. female**	37(67.3%) 18(32.7%)	35(63.6%) 20(36.4%)	0.841
Diabetics	36(61%)	23(39%)	**0.036**
Hypertensives	9(45%)	11(55%)	
Dyslipidemia	2(66.7%)	1(33.3%)	
Alcohol	1(1.8%)	6(10.9%)	**0.02**
Tobacco	17(30.9%)	14(25.5%)	**0.03**
Alcohol and tobacco	17(30.9%)	11(20%)	**0.001**
Family History	13(68.4%)	6(31.6%)	0.077
STEMI	34(48.6%)	36(51.4%)	0.542
NSTEMI	18(58.1%)	13(41.9%)	
Unstable angina	1(50%)	1(50%)	
GENSINI SCORE	35.53 ± 17.84	20.56 ± 13.66	**0.001**
CTO	18(32.7%)	8(14.5%)	**0.001**
LMCA Stenosis	9(16.4%)	0	**0.001**
Critical lesions	44(80%)	39 (70.9%)	0.267

Table 2: Relationship of Serum uric acid with severity of CAD

Severity of CAD	**Number**	**Mean SUA (mg%)**
SVD	33(30%)	5.56±1.98
DVD	29(26.4%)	6.03±1.72
TVD	43(39.09%)	6.53±1.82
LMCA	5 (4.54%)	7.32±0.84

p=0.001, r=0.856

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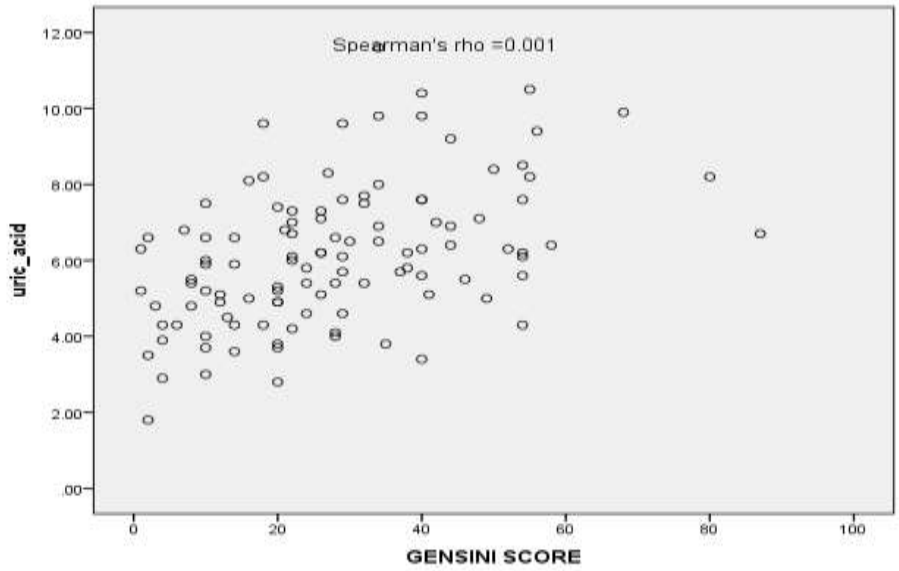
Figure 1: Scatter plot for correlation between Gensini score and serum uric acid



DISCUSSION

In all industrialized countries, cardiovascular illnesses, particularly acute coronary syndrome, continue to be the primary cause of death despite advancements in treatment procedures. Age and sex are examples of proven non-modifiable risk factors. Modifiable risk factors, on the other hand, include diabetes, hypertension, smoking, dyslipidemia, and diabetes. These factors are what cause the disease process and only partially explain mortality. Therefore, it is imperative to look for additional risk factors that indicate the severity of the condition so that the appropriate course of therapy may be determined.(22)

The main findings of this study are as follows:

i. The proportion of male patients with coronary heart disease having hyperuricemia were greater than that of female hyperuricemic patients , and serum uric acid was found to be elevated in patients with hypertension, diabetes, dyslipidemia, tobacco chewing, and alcoholism.

ii. Gensini score was found to be higher in patients with increased uric acid levels as compared to patients with normal uric acid level.

iii. Gensini score was positively associated with serum uric acid. Hence higher the uric acid levels, greater is the Gensini score, which signifies greater is the severity

iv. of coronary lesions in terms of critical lesions and total occlusion.

v. The serum uric acid level co related with severity of CAD. The severity of CAD is assessed using the Gensini score .

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vi. Patients with raised serum uric acid level manifested with greater number of critical lesions

vii. Patients with higher serum uric acid was found to have higher number of chronic total occlusion in contrast to patients with normouricemia

viii. On coronary angiography One-vessel, 2-vessel, and 3-vessel disease, left main coronary artery stenosis was diagnosed in 30%, 26.4%, and 39.09%, 4.54% of the patients, respectively

ix. As the severity of lesions ranged from single to double, and triple vessel disease the serum uric levels also demonstrated an increasing trend.

Tian et al. conducted a population based cohort study which stated that uric acid levels were associated with the presence and severity of CAD. Uric acid level may be involved in the progression of CCS.(23) Mehmet et al. carried out a prospective cohort study which concluded that elevated Uric acid levels on admission are independently associated with impaired coronary flow after primary PCI and both short-term and long-term outcomes in patients who undergo primary PCI for the management of STEMI.(24)

Given that inflammation is a major cause of coronary artery disease and that anti-inflammatory drugs like colchicine may offer an additional therapeutic advantage, recent clinical data have demonstrated the therapeutic impact that addressing inflammatory pathways might play in improving outcomes for patients with ACS.(25) When patients with ACS and stable CAD received colchicine 0.5 mg/d in addition to standard secondary prevention therapies, as opposed to standard medical therapy alone, there was a significant decrease in adverse cardiovascular events, as shown by the COLCOT (Colchicine Cardiovascular Outcomes Trial) and LoDoCo (Low Dose Colchicine for Secondary Prevention of Cardiovascular Disease) trials.(26,27)

These findings are consistent with earlier research showing that patients with ST-segment-elevation myocardial infarction (STEMI) receiving primary percutaneous coronary intervention have smaller infarct sizes and significantly lower levels of inflammatory cytokines in ACS after receiving short-term colchicine therapy.(28,29) Patients with stable coronary disease who received colchicine at a dose of 0.5 mg once day experienced fewer cardiovascular events than those who did not get colchicine, according to the Low-Dose Colchicine (LoDoCo) trial.(30) The main outcome of cardiovascular death, spontaneous myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization was consistently reduced by colchicine. A slightly significant impact of colchicine was observed on the decrease in hs-CRP serum levels. Colchicine dramatically lowered the incidence of

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major adverse cardiovascular events (MACE) in CAD patients undergoing PCI, mostly through reducing stent thrombosis and recurrent artery revascularization. Independent of significant low-density lipoprotein reduction and high-dose statin intensification therapy, low-dose colchicine therapy favorably changes coronary plaque .If confirmed in more research, colchicine might be helpful as an extra secondary preventive medication in people who have had ACS.(31)

Numerous recent investigations have indicated that uric acid may be connected with the presence of CAD (32), despite findings from the Framingham Heart Study and ARIC study showing no connection between uric acid and CAD. Elevated Serum Uric Acid Levels in Acute Coronary Syndrome Patients May Predict Severity of Coronary Artery Disease, according to Mustafa Duran et al. and Berkay Ekici et al.'s findings.(33) A study by Freedman DS et al. showed a connection between serum uric acid and ischemic heart disease as well as death. Studies by Troy E. Madsen et al. found that in patients with significant, angiographically defined coronary disease, serum uric acid independently predicts mortality.(34) It was determined that elevated serum uric levels constitute a separate risk factor for individuals with high cardiovascular risk.(35)

LIMITATIONS OF THE STUDY

Intravascular ultrasound was not performed on the participants in this investigation to determine the amount of atherosclerotic coronary plaque. Second, individuals visiting a single center for coronary angiography do not necessarily represent the entire community. A prognostic significance follow-up and analysis of the impact of changing uric acid levels, which would represent the mortality linked to CAD, would also be intriguing. To get further details, large-scale prospective researches are required. Confounding factors include the metabolic syndrome, obesity, diabetes, and hypertension, which have been linked to elevated uric acid levels.

CONCLUSION

In summary, our study found an independent relationship between the severity and complexity of CHD and serum uric acid levels. Hyperuricemia was linked to angiographically confirmed CAD, according to research done on patients receiving coronary angiography. In addition to other risk factors, this straightforward biochemical test can be utilized in routine clinical practice to assess the burden of cardiovascular disease in relation to the correlation between the SUA levels and the severity of CHD. To determine if SUA levels acquired during regular testing are more valuable for diagnosis, risk assessment, and therapy evaluation in individuals with atherosclerotic CHD, large-scale prospective, randomised

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clinical trials are required. There may be new approaches to the diagnosis, management, and prevention of coronary heart disease.

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