Serum Uric Acid in Acute Coronary Syndromes

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ABSTRACT

Introduction: Uric acid (urate), an organic compound of carbon, nitrogen, oxygen and hydrogen has been thought to be protective against ageing, oxidative stress and oxidative cell injury owing to its oxidant property. Recent epidemiological and clinical evidences suggest that hyperuricaemia might be a risk factor for cardiovascular disease where enhanced oxidative stress plays an important pathophysiological role. The study is taken up to determine serum uric acid levels in Acute Coronary Syndromes (ACS) and to compare the incidence of complications in hyperuricaemic and normouricaemic acute coronary syndrome patients.

Material and Methods: A prospective cohort study was conducted in the Department of Medicine in collaboration with Department of Biochemistry, RIMS, Imphal from October 2014 to September 2016, among 73 normouricaemic ACS patients and 73 hyperuricaemic ACS patients. Clinical and anthropometric data were taken from each subject. Laboratory evaluation involves serum uric acid by enzymatic colorimetric method.

Results: The mean serum uric acid level in the study population was 5.96 ± 1.88 mg/dl. Arrhythmias occurred in 27.4% of hyperuricemic patients and 5.5% of normouricemic patients. It is observed that 27 patients developed congestive cardiac failure (CCF), out of which 17 patients (22.3%) were hyperuricaemic and 10 patients (13.7%) were normouricaemic. Pulmonary edema (PE) was observed in 35 hyperuricaemic and 28 normouricaemic patients (47.9% and 38.4% respectively).

Conclusions: Complications of ACS such as arrhythmias, CCF and PE occurred more frequently in hyperuricaemic individuals. Thus, it can be concluded that serum uric acid level can be considered a suitable marker for predicting ACS-related future adverse events.

Keywords: Acute Coronary Syndrome, Arrhythmia, Congestive Cardiac Failure, Hyperuricaemia, Pulmonary Edema.

INTRODUCTION

Ischaemic heart disease (IHD) causes more deaths and disability and incurs greater economic costs than any other illness in the developed world. Population subgroups that appear to be particularly affected are men in South Asian countries, especially India and the Middle East. In light of the projection of large increases in IHD throughout the world, IHD is likely to become the most common cause of death worldwide by 2020.[1]

Patients with ischaemic heart disease fall into two large groups: patients with Coronary Artery Disease (CAD) who most commonly present with stable angina and patients with Acute Coronary Syndromes (ACS). These include patients with acute myocardial infarction with ST segment elevation (STEMI) on their presenting electrocardiogram and those with non ST elevation ACS (NSTE-ACS) which include patients with non ST elevation myocardial infarction (NSTEMI) who have myocyte necrosis, and, those with unstable angina (UA) who do not.[2]

Uric acid (urate), an organic compound of carbon, nitrogen, oxygen and hydrogen, is the final oxidation product of purine metabolism, and its elevated levels reflect increased xanthine oxidase activity. For decades it has been hypothesised that the oxidant properties of uric acid might be protective against ageing, oxidative stress and oxidative cell injury. However, recent epidemiological and clinical evidences suggest that hyperuricaemia might be a risk factor for cardiovascular disease where enhanced oxidative stress play an important pathophysiological role.[3] It has been recently reported that serum uric acid is an independent predictor of mortality for patients with coronary artery disease (CAD) and morbidity, including acute myocardial infarction (AMI) or congestive heart failure (CHF).[4,5,6,7]

Hyperuricemia is present frequently in patients with symptomatic heart failure, acute coronary syndromes, arterial hypertension, and atrial fibrillation.[8,9,10] It has been postulated that serum uric acid plays a pivotal role in the pathogenesis of cardiovascular diseases affecting xanthine oxidase pathway that contributes to the production of reactive oxygen species with deterioration of cell membranes[11]. Reactive oxygen species contribute to vascular oxidative stress and endothelial dysfunction, which are associated with the risk of atherosclerosis, damages of both cardiomyocytes and

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vascular endothelium inducing disturbances of myocardial contractility and vasoconstriction.[12] The increase in serum uric acid in patients with cardiovascular disease may reflect a compensatory mechanism to counter the oxidative stress that occurs with tissue hypoxia, thus, the higher levels of uric acid corresponding to high risk may reflect response to tissue injury, whereas the higher risk at lower levels of uric acid levels may be the result of decreased antioxidant capacity.[13,14,15]

Evidence for involvement of uric acid in cardiovascular disease is extensive, and so are the controversies surrounding the interpretation of the data.[14,15,16,17] This study has been taken up to determine serum uric acid levels in Acute Coronary Syndromes (ACS) and to compare the incidence of complications in hyperuricaemic and normouricaemic ACS patients.

MATERIAL AND METHODS

This prospective cohort study was conducted in the Department of Medicine in collaboration with Department of Biochemistry, Regional Institute of Medical Sciences (RIMS), Imphal, Manipur, from October 2014 to October 2016. Study was approved by the Institutional Ethical Committee, Regional Institute of Medical Sciences, Imphal and all the participants gave written informed consent prior to the study.

Study population comprised of 146 patients aged >18 years with acute coronary syndromes admitted in ICCU, RIMS, irrespective of race and sex. Acute coronary syndromes include symptomatic ACS, unstable angina, STEMI and NSTEMI. The study participants were divided into 2 groups: 73 patients of ACS with normal serum uric acid levels (normouricaemic) and 73 ACS patients with elevated serum uric acid levels (hyperuricaemic). Patients with symptomatic chronic heart failure, uncontrolled diabetes mellitus, severe kidney and liver diseases, malignancies, brain injury within 3 months before enrolment, pulmonary infections, surgery, trauma or inflammatory conditions within 1 month and pregnant women were excluded from the study.

Each individual enrolled in the study underwent a detailed history taking, general physical examination, systematic examination and routine investigations like complete blood count, liver function test, random blood sugar and uric acid. Five ml of venous blood was collected from each individual in the first 48 hours after admission. Serum uric acid was measured by enzymatic colorimetric method as described by Fossati P et al[18] using Randox kit by Randox series RX Imola Autoanalyser (Manufactured 2007, United Kingdom).

RESULTS

Table 1 shows the general characteristics and mean serum uric (SUA) levels in the study groups. There was a male preponderance in the study group (61% and 39% in males and females respectively). Out of the total 146 patients, 67

	Normouricaemic	Hyperuricaemic	Total
Female	25(34.2%)	32(43.8%)	57(39%)
Male	48(65.8%)	41(56.2%)	89(61%)
Smoking	33(45.2%)	34(46.6%)	67(45.9%)
Alcohol	19(26%)	17(23.3%)	36(24.7%)
Mean SUA ± SD (mg/dl)	4.43±1.21	7.49±0.94	5.96±1.88
Table-1: General characteristics and mean SUA levels in the study groups			

Age in years	Normouricaemic	Hyperuricaemic	Total
<30	0(0%)	1(1.4%)	1(0.7%)
30-40	5(6.8%)	4(5.5%)	9(6.2%)
41-50	12(16.4%)	20(27.4%)	32(21.9%)
51-60	28(38.4%)	32(43.8%)	60(41.1%)
61-70	23(31.5%)	8(11%)	31(21.2%)
71-80	4(5.5%)	8(11%)	12(8.2%)
>80	1(1.4%)	0(0%)	1(0.7%)
Total	73(100%)	73(100%)	146(100%)
Mean ± SD	57.47±10.03	55.67±10.75	56.57±10.40
Samples are age matched with P=0.299			
Table-2: Age distribution of patients studied			

Killip Class	Normouricaemic	Hyperuricaemic	Total
1	44(60.3%)	37(50.7%)	81(55.5%)
2	22(30.1%)	21(28.8%)	43(29.5%)
3	7(9.6%)	11(15.1%)	18(12.3%)
4	0(0%)	4(5.5%)	4(2.7%)
Total	73(100%)	73(100%)	146(100%)
P=0.363, not significant, Fisher Exact test			
Table-3: Killip Class distribution in two groups of patients studied			

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BMI (kg/m²)	Normouricaemic	Hyperuricaemic	Total
<18.5	0(0%)	2(2.7%)	2(1.4%)
18.5-25	54(74%)	56(76.7%)	110(75.3%)
25-30	19(26%)	14(19.2%)	33(22.6%)
>30	0(0%)	1(1.4%)	1(0.7%)
Total	73(100%)	73(100%)	146(100%)
Mean ± SD	24.12±1.99	23.33±2.27	23.73±2.17
P=0.029*, significant, student t test			

Table-4: BMI (kg/m2) distribution in two groups of patients studied

|	Normouricaemic	Hyperuricaemic	Total	*P* value
Arrhythmias**	4(5.5%)	20(27.4%)	24(16.4%)	<0.001
CCF	10(13.7%)	17(23.3%)	27(18.5%)	0.136
Pulmonary edema	28(38.4%)	35(47.9%)	63(43.2%)	0.242
P< 0.001**, significant, Chi-square test				

Table-5: Incidence of arrhythmias, CCF and pulmonary edema (PE) in the two groups of patients studied

Outcome at discharge	Normouricaemic	Hyperuricaemic	Total
<7	50(68.5%)	36(49.3%)	86(58.9%)
7-14	20(27.4%)	29(39.7%)	49(33.6%)
>14	3(4.1%)	8(11%)	11(7.5%)
Total	73(100%)	73(100%)	146(100%)
P=0.094+, Significant, Fisher Exact test			

Table-6: Outcome at discharge incidence in two groups of patients studied
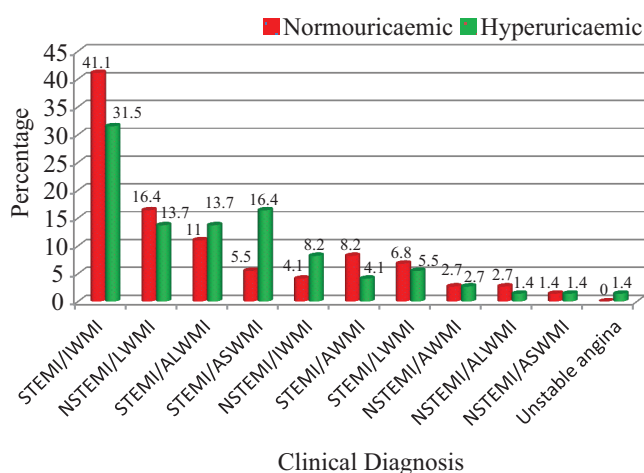
Figure-1: Clinical Diagnosis in two groups of patients studied

(45.9%) were smokers and 36 (24.7%) used alcohol. The mean SUA level in the study population was 5.96±1.88 mg/dl. Normouricaemic patients had mean SUA levels 4.43±1.21 mg/dl, while mean SUA levels in hyperuricaemic patients was 7.49±0.94 mg/dl.

Table 2 shows that the most common age group in ACS was 51-60 years (41.1%) in both normouricaemic and hyperuricaemic individuals (38.4% and 43.8% respectively) and the mean age in the study population was 56.57±10.40 years (57.47±10.03 in normouricaemic and 55.67±10.75 in hyperuricaemic groups respectively).

Figure 1 shows that the most common clinical diagnosis among the patients with ACS was STEMI/IWMI followed by NSTEMI/LWMI, STEMI/ALWMI, STEMI/ASWMI (36.3%, 15.1%, 12.3% and 11% respectively) comparable across the study population and the least common occurrence

was that of Unstable Angina in only one patient with Hyperuricaemia.

Table 3 shows Killip Class Functional Classification across the study groups. Majority of patients belonging to both study groups could be grouped into the Class 1 Killip Functional Classification (55.5%) followed by Killip Class 2 (29.5%) and Killip Class 3 (12.3%), comparable across the study groups. However, Killip Class 4 Functional Classification was observed only in 4 patients belonging to the hyperuricaemic group of individuals (5.5%).

Table 4 shows the relation between BMI and ACS in the study groups. Majority of the patients were categorised into the BMI category 18.5-25 i.e, 110 patients (75.3%); 54 normouricaemic and 56 hyperuricaemic (74% and 76.7% respectively). Mean BMI in normouricaemic and hyperuricaemic individuals was 24.12±1.99 kg/m² and 23.33±2.27 kg/m² respectively.

Table 5 shows the occurrence of arrhythmias, congestive cardiac failure (CCF) and pulmonary edema across the study groups. Arrhythmias occurred in 24 patients (16.4%) in general, out of which 20 patients were hyperuricaemic as compared to 4 patients who were normouricemic (27.4% and 5.5% respectively). It was observed that total 27 patients (18.5%) developed CCF, out of which 17 patients (22.3%) were hyperuricaemic and 10 patients (13.7%) were normouricemic. Pulmonary edema was observed in 63 patients (43.2%), out of which 35 patients were hyperuricaemic and 28 patients were normouricaemic (47.9% and 38.4% respectively).

Table 6 charts the outcome at discharge incidence in the study groups. All 146 patients improved during hospital stay, though varying in duration. 86 patients (58.9%) were

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discharged within a week of admission, out of which, 50 were normouricaemic while 36 were hyperuricaemic (68.5% and 49.3% respectively). 49 patients (33.6%) were discharged within 2 weeks of admission, wherein, 20 were in the normouricaemic group and 29 in the hyperuricaemic group (27.4% and 39.7% respectively). 11 patients (7.5%) were hospitalized for almost 4 weeks, but eventually discharged, among them 3 were normouricaemic and 8 hyperuricaemic (4.1% and 11% respectively).

Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for analysis of the data. Results on continuous measurements were presented on Mean ± SD and results on categorical measurements were presented in number (%). Student t test was used to find the significance of study parameters on continuous scale between two groups on metric parameters. Chi-square/ Fisher Exact test was used to find significance of study parameters on categorical scale between two or more groups.

DISCUSSION

The present study showed that the most common age group at which patients suffered ACS was 51-60 years (41.1%) in both norrmouricaemic and hyperuricaemic individuals (38.4% and 43.8% respectively) with the mean age 56.57±10.40 years (57.47±10.03 in normouricaemic and 55.67±10.75 in hyperuricaemic groups respectively).

The study observed a male preponderance in the incidence of ACS overall as compared to females (61% vs 39%). However, SUA levels was found to be elevated in females more than in males, which was similar to a study conducted by Short RA et al[19] and Strasak AM et al[9] where females were observed to have higher incidence of hyperuricaemia as compared to males.

Majority of patients belonging to both study groups could be grouped into the Class I Killip Functional Classification (55.5%) followed by Killip Class II (29.5%) and Killip Class III (12.3%), comparable across the study groups. However, Killip Class IV Functional Classification was observed only in 4 patients of the hyperuricaemic group of individuals (5.5%). There were no mortalities in the present study. The findings in this study concur with that conducted by Kojima S et al[5] wherein the study results suggested that hyperuricaemia after AMI is associated with the development of heart failure. Serum uric acid level could, therefore, be considered a suitable marker for predicting AMI-related future adverse events, and the combination of Killip's class and serum uric acid level after AMI is a good predictor of morbidity and mortality in patients who have AMI.

In the present study, out of the 146 patients studied 45.9% had smoking and 24.7% alcohol use as risk factors and comparable across the study groups. Though considered as significant risk factors for ACS, the results, however, were not statistically significant to correlate the SUA levels to the severity of complications.

There is a common concept that patients with a higher BMI kg/m² are more likely to suffer ACS and CAD. In this study,

however, it was observed that patients in the normal BMI range of 18.5-25 kg/m² suffered from ACS with a slightly higher number of patients in the hyperuricaemic group than in the normouricaemic group (76.7 vs 74%). This is in concurrence with a study conducted by Okura T et al[20], wherein, the association of elevated serum uric acid (UA) with cardiovascular events in patients with severe coronary artery stenosis was examined and elevated UA was found to be an independent predictor of cardiovascular events and all-cause mortality in patients with normal BMI ranges.

Arrhythmias, congestive cardiac failure (CCF), pulmonary oedema (PE), stroke and death are proven complications of ACS. In our study, arrhythmias occurred in 24 patients (16.4%) in general, out of which 20 patients were hyperuricaemic as compared to 4 patients who were normouricaemic (27.4% vs 5.5%). Similar findings were seen in a study conducted by Ioachimescu AG et al[21] who evaluated the prognostic value of serum uric acid levels in a large cohort of men and women at high risk of cardiovascular disease. In it, patients with elevated levels of uric acid were found to have more incidences of complications as compared to those who were normouricaemic. However, further studies are required to prove the association as the sample size may not be a representative of the entire population. CCF was observed in 18.5%, out of which hyperuricaemic individuals were more prone to develop CCF than normouricaemic individuals (22.3% vs13.7%). PE was observed in 43.2% of patients as a whole, however hyperuricaemic patients were found to be at a significantly higher risk of developing PE when compared to normouricaemic patients (47.9% vs 38.4%). Similarly, in studies conducted by Chen JH et al[22], Jelić-Ivanović Z et al[23],Wang JW et al[24], the investigators also observed higher incidences of Major Adverse Cardiovascular Events (MACE), in hyperuricaemic patients as compared to normouricaemic patients.

In the present study, all 146 patients improved during hospital stay, though varying in duration. Out of which 58.9% were discharged within a week of admission, more in the normouricaemic than hyperuricaemic (68.5% vs 49.3%); 33.6% were discharged within 2 weeks of admission, majority of whom were in the hyperuricaemic group as compared to normouricaemic group (39.7% vs 27.4%); 7.5% were hospitalized for almost 4 weeks, but eventually discharged, among them maximum patients were hyperuricaemic (11% vs 4.1%) and had a protracted course of illness and was statistically significant.

CONCLUSION

The present study showed that complications of ACS such as arrhythmias, CCF, PE occurred more frequently in hyperuricaemic individuals as did the severity of Killip Class functional classification. Majority of the patients in the normouricaemic group had an uneventful hospital stay and recovered earlier as compared to those in the hyperuricaemic group, who experienced a longer duration of hospitalisation with higher incidences of complications. Thus it can be concluded that serum uric acid level, a relatively inexpensive

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and widely available biomarker, could be considered a suitable marker for predicting ACS-related future adverse events, and the combination of Killip's class and serum uric acid level is a good predictor of risk stratification in patients who present with ACS.

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