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Association of Hyperuricemia with Acute Coronary Syndrome, Complications and Outcome

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Abstract
The purpose of this study was to demonstrate the relationship between serum uric acid level and major adverse cardiovascular events during admission and 30-day period after admission across the whole spectrum of acute coronary syndrome (ACS).Total 176 patients with new onset ACS were included in the study. Patients with prior history of coronary artery disease, chronic liver or kidney disease, any malignancy and patients on drugs affecting serum uric acid levels were excluded. Routine laboratory investigations, resting 12 lead ECG and ECHO cardiography were done for all patients. Serum uric acid (SUA) was obtained within 24 hours of admission. The patients were divided into two groups: Group I: 41 patients with elevated serum uric acid (>8.2 mg/dl in males and >6.1 mg/dl in females); Group II: 135 patients with normal serum uric acid levels. We monitored the patients in the hospital and followed the patients for 30 days for the occurrence of major adverse cardiovascular events (MACE). The incidence of MACE and mortality were significantly higher in patients with hyperuricemia than in patients with normal serum uric acid during hospital stay and 30 days follow-up ($p<0.05$). There was a statistically significant correlation between high serum uric acid level and higher Killip class on day of admission. Multivariate logistic regression analysis of data showed a significant difference between group I and II, confirming that SUA can be utilised as a useful biomarker for predicting short-term mortality and MACE in patients with ACS.

Introduction

Acute coronary syndrome (ACS) is a unifying term representing a common end result, acute myocardial ischemia. It encompasses acute myocardial infarction (resulting in ST elevation myocardial infarction i.e. STEMI or non-ST elevation myocardial infarction i.e. NSTEMI) and unstable angina. Cardiovascular diseases (CVDs) account for >17 million deaths globally each year (30% of all deaths), 80% of which occur in low-income and middle-income countries, and this figure is expected to grow to 23.6 million by

2030.[1] Since the underlying pathophysiology of disease in patients with ACS varies widely, accurate risk stratification to determine appropriate management and improve outcomes is essential.

As such, the use of prognostic biomarkers may facilitate the ability to anticipate complications following MI and provide timely preventive care to at-risk individuals. The Diagnostic Marker Cooperative Study in 1999 evaluated the role of these biochemical markers in the evaluation of ACS patients.CK-MB isoforms and myoglobin were found to be the most efficient for diagnosis, whereas both cardiac troponins proved to be the most cardiac specific and were very useful for the late diagnosis of MI as their levels usually remain elevated for 7–14 days.[2] These markers have specific temporal profile in relation to MI; however, the levels of these enzymes do not correlate with myocardial function and the complications resulting with ACS

Uric acid is produced by the enzymatic activity of xanthine oxidase and is the final product of purine metabolism.Xanthine oxidase activity and uric acid synthesis are increased in vivo under ischaemic conditions, and therefore elevated serum uric acid may act as a marker of underlying tissue ischaemia.[3] Epidemiological studies have shown that increased uric acid is significantly associated with the occurrence and mortality of coronary artery disease.[4] Some evidences suggest that uric acid may exert a negative effect on cardiovascular disease by stimulating inflammation. According to a recent study done in Japan by Kojima *et al* (Japanese Acute Coronary Syndrome Study), a univariate association was found between higher serum uric acid (SUA) on admission (within 48 hours since the symptom onset) and higher thirty-day mortality (fourth vs. first quartile SUA values) in AMI patients. It also reported an independent association between higher SUA and poorer long-term survival. There was a close correlation between serum uric acid concentration and Killip class in patients of acute myocardial infarction.[5]There are various other studies on association of SUA levels with in-hospital complications and long term survival in patients presenting with acute myocardial infarction. According to much research, uric acid could be a marker of adverse prognosis in patients with acute myocardial infarction though there are other studies that showed no relation between serum uric acid level and mortality rate.[6]Most of the studies so far have evaluated the relation of serum uric acid with STEMI and did not cover the whole acute coronary syndrome spectrum i.e. unstable angina and NSTEMI. As very few studies on the correlation of uric acid with ACS have been conducted in India and none from this part of the country so far, we carried out this cohort study to note levels of serum uric acid in acute coronary syndromes, to correlate serum uric acid levels with Killip class and to note any relationship between serum uric acid level, MACE, mortality or complications in the hospital during admission, and on follow up after 30 days.

Methods

This study was conducted in the Department of Medicine and Cardiology, Indira Gandhi Medical College, Shimla. One hundred seventy six patients with acute coronary syndrome admitted to coronary care unit (CCU) between July 1, 2014 and June 30, 2015 were included. This was a prospective study and the study protocol was approved by the local ethics committee. Informed consent was obtained from the patients. All new patients with acute coronary syndrome more than 18 years age andfrom both genders were selected.

Patients were excluded if they had[1] Previous history of ACS[2] Conditions altering serum uric acid levels including chronic kidney disease, liver disease, gout, alcoholism, violent exercise, hematological malignancy, patients on chemotherapy for malignancies.[3] history of intake of drugs that may alter serum uric acid levels, like loop diuretics, thiazide diuretics, indapamide, metolazone, salicylates, ethambutol, amiloride, cisplatin, cyclosporine, cyclophosphamide, ethacrynic acid, ketoconazole,

levodopa, pentamidine, phencyclidine, pyrazinamide, theophylline, vitamin C[4]
Unwillingness to participate in the studyPatients were assessed by relevant history, clinical examination with special reference to Killip class, ECG findings, troponin T (where indicated), and lipid profile. Echocardiography was performed by the Cardiologist using standard imaging planes according to the recommendations of the American Society of Echocardiography. Serum uric acid level was done within 24 hours of admission and patients were divided into two groups:

Group I: Those having high serum uric acid levels
Group II: Those having normal serum uric acid levels.

(Normal range as per our laboratory being 2.3-6.1mg/dl in females and 3.6-8.2mg/dl in males); done by enzymatic, calorimetric technique using auto analyzer. Patients in both the groups were observed for the development of complications; MACE during the hospital stay and on 30 days follow up. Weanalyzed data using SPSS version 16 and Epi Info version 7.0.9 for windows. We calculated the association between uric acid levels and different sequelae, complications and outcome by RR (Relative risk) and 95% confidence intervals of RR. Stratified analysis was carried to adjust for the effects of potential effect modifiers (like diabetes and hypertension). Multivariate analysis was carried to adjust for the effect of potential confounders. A p-value of ≤0.05 was treated as statistically significant.

Results

The age of study population ranged from 29 to 98 years and mean age was 60.6 ± 12.8 years. The mean age of men was 59.3±13.3 years and for women, it was 64.3±10.3 years. Among all the study participants, 130 (74%) were men and 46 (26%) were women. Smoking was the most frequent risk factor observed; 121 (69%) out of total 176 patients were smokers. 24 (7%) participants were known patients of Diabetes mellitus, 40(23%) patients had hypertension and 40(23%) had obesity. Low HDL was noted in 105 (60%) patients and hypertriglyceridemia was present in 63 (36%) patients. After stratifying patients into high and normal uric acid groups, it was observed that 78% in hyperuricemia group had low HDL as compared to 54% in normal uric acid group ($p < 0.05$). Clinical and biochemical characteristics of patients in the two groups are shown in Table 1. There was a statistically significant difference between two groups as regarding serum uric acid level (9.5±2.2 in group I vs 5.8±1.2 in group II; $p<0.0001$), serum creatinine (1.43±0.8 in group I vs 0.96±0.3 in group II; $p <0.001$) and blood urea levels (53.7±29.6 in group I vs 33.6±14.2 in group II, $p<0.001$). Rest of the characteristics were comparable between the two groups.

In patients with ST EMI (n =113), 71 patients were in Killip Class I, 22 in Killip Class II, 6 in Killip Class III and 14 in Killip Class IV. Thirteen out of 14 patients in Class IV and 5 of 6 patients in Killip Class III were hyperuricemic and hyperuricemia was associated with higher Killip Classes, III and IV ($p<0.05$). Majority (78%) of patients in hyperuricemic group presented with ST elevated MI ($p<0.05$). There was no significant difference between two groups as regards territory of ischemia. The mean LV ejection fraction was 46.39±14.5 in group I and 62.6±9.90 in group II ($p <0.05$).Of total 176 patients, 32 patients with high SUA and 8 patients with normal SUA developed complications [total 40(23%) patients developed complications)] during the hospital stay, out of which 25 (22%) developed heart failure, 4 (2%) developed arrhythmias, 4 (2%) developed each arrhythmia and cardiogenic shock. Seven (4.0%) patients died during hospital stay. Thirty two out of 40 (80%) patients who developed complications were in hyperuricemic group ($p<0.05$). Of 7 patients who died during the hospital stay, 6 were having hyperuricemia and 169 patients were discharged from the hospital.

Patients were followed up after 30 days of discharge from hospital, 12 of these 169 patients developed complications. Eight (5%) patients

developed heart failure, 2 (1%) patients suffered from second episode of ACS and remaining 2 (1%) patients died. Majority 11 (91.6%) patients developing complications and both the patients who died were hyperuricemic. Table 2 shows the incidence of complications according to the selected characteristics. Significant association was seen between the incidence of complications and older age (>60 years), female sex, presence of higher Killip classes (III and IV) and high uric acid ($p<0.05$ in all). Multivariate logistic regression analysis of data after adjusting for age, sex, presence of ST elevation and higher Killip Class (III and IV) showed a significant difference between group I and II and uric acid was confirmed as an independent predictor for in-hospital mortality and MACE [odds ratio:37.7 (95% confidence interval : 11.6-123.0)] (Table 3)

Table 1: Clinical, Biochemical, ECG and ECHO cardiographic characteristics of two groups

	Hyperuricemia Group I (n=41)	Normal Uric Acid Group II (n=135)	p value
Mean age (years)	64.9±11.2	59.2±13.0	0.012
Male (n) **Female (n)**	21 (51%) 20 (49%)	109 (81%) 26 (19%)	<0.001
Smoking (n)	30 (73%)	91 (67%)	0.485
Diabetes Mellitus (n)	6 (15%)	18 (13%)	0.831
Hypertension(n)	12 (29%)	28 (21%)	0.254
Obesity (n)	8 (19%)	32 (24%)	0.574
Dyslipidemia (n) High TG Low HDL	 15 (37%) 32(78%)	 48 (36%) 73 (54%)	 0.904 0.006
Killip Class(n) I II III IV	 7 (22%) 7(22%) 5(16%) 13(41%)	 64 (79%) 15 (18%) 1(1%) 1 (1%)	 <0.001
Territory of ischemia Anterior (n) inferior±right posterior lateral	 25 (61%) 13(32%) 0 1 (2%)	 60 (44%) 57 (42%) 1 (7%) 15 (11%)	 0.128
LVEF (%)	46.39±14.5	62.6±9.9	<0.001
FBS (mg/dl)	116.1±52.2	109.7±48.9	0.472
Blood urea(mg/dl)	53.7±29.6	33.6±14.2	<0.001
Serum creatinine(mg/dl)	1.43±0.8	0.96±0.3	<0.001
Serum uric acid(mg/dl)	9.5±2.2	5.8±1.2	<0.001
Cholesterol(mg/dl)	165.8±43.0	175.3±39.9	0.195
Triglycerides(mg/dl)	140.2±58.8	143.8±74	0.777
HDL(mg/dl)	38.4±9.0	39.9±8.0	0.308
LDL(mg/dl)	98.2±31.7	107.7±34.2	0.115

Table 2: Incidence of Complications/Death Post- hospitalization till 30 day follow-up

	Incidence of complications/death						Relative risk	95% confidence interval	p-value
	Among exposed (high uric acid)			Among unexposed (normal uric acid)					
	#	Total	%	#	Total	%			
Age> 60	28	82	34	12	94	13	2.7	1.5-4.9	0.001
Female sex	20	46	43	20	130	15	2.8	1.7-4.8	<0.001
ST Elevation	30	113	26	10	63	16	1.7	0.9-3.2	0.105
Smoking	26	121	21	14	55	25	0.8	0.5-1.5	0.561
Diabetic mellitus	9	24	37	31	152	20	1.8	1.0-3.4	0.063
Hypertension	12	40	30	28	136	21	1.5	0.8-2.6	0.212
Systolic hypertension	5	29	17	35	147	24	0.7	0.3-1.7	0.440
Diastolic hypertension	6	45	13	34	131	26	0.5	0.2-1.1	0.081
Both systolic and diastolic hypertension	5	27	18	35	149	23	0.8	0.3-1.8	0.571
Abdominal obesity	18	74	24	22	102	22	1.1	0.7-2.0	0..667
Raised Triglycerides (≥150mg/dL)	14	63	22	26	113	23	1.0	0.5-1.7	0.905
Low HDL	7	105	7	2	71	3	2.4	0.5-1.1	0.255
Killip Class III/IV *	16	17	94	14	96	15	6.5	3.9-10.6	<0.001
High uric acid	33	41	80	7	135	5	15.5	7.4-32.4	<0.001

*calculated for ST elevated Acute Coronary syndrome (complications/death=30 out of 113). For all other calculations n=176.

Table 3: Multivariate logistic regression analysis of risk of complications with different risk factors among patients of acute coronary syndrome

Risk factor	Odds ratio	95% confidence interval		p-value
		Lower bound	Upper bound	
Age> 60	2.8	0.8	9.8	0.102
Sex (M/F)	0.5	0.1	1.8	0.293
ST Elevation	1.0	0.3	3.7	0.971
Killip Class III and IV	14.4	1.3	163.0	0.032
High Uric Acid	37.7	11.6	123.0	<0.001

Discussion

In our study, older age and female gender correlated with high serum uric acid levels. A study by Kojima *et al*[10] in 2005, however, noted that male gender correlates with hyperuricemia. This difference between our study and previous studies could be because of various reasons: majority of our study population was rural; and women, especially in villages, tend to take their symptoms less seriously and only the complicated ones present to hospital very late. Moreover, women often have more atypical symptoms, thus, delaying the diagnosis and presentation to hospital. However, there was significant correlation between low HDL and high uric acid levels ($p<0.05$). Li Chen et alfound that hyperlipidemia was more common in hyperuricemic patients.[7] There was no significant correlation of smoking, presence of diabetes mellitus, hypertension, obesity and high triglyceride levels with serum uric acid levels.

ST elevation was present in 113 (64.2%) patients of ACS in our study. The presence of ST elevation correlated with high SUA on admission, but there was no correlation between serum uric acid levels and the territory of ischemia/ infarction. There was a significant correlation between presence of severe LV systolic dysfunction and high serum uric acid ($p<0.05$). Kowalczyk *et al*[8] observedthat in-hospital, 30-day, 1-year and entire-period all-cause mortalities were higher in hyperuricemic patients. Multivariate logistic regression analysis of data after adjusting for age, sex, presence of ST elevation, and higher Killip Class (III and IV) showed a significant difference between group I and II and uric acid was confirmed as an independent predictor for in-hospital mortality [odds ratio:37.7 (95% confidence interval : 11.6-123.0)]

Bae MH investigated 850 patients with AMI and concluded that SUA was an independent predictor of short-term prognosis and had incremental prognostic value to conventional risk factors (chi-square=8, p=0.005), and to the combination of conventional factors and NT-Pro BNP (chi-square=10, p=0.002).[9] Kojima *et al* evaluated 1,124 consecutive patients, hospitalized within 48 hours of onset of symptoms of AMI. Serum uric acid level was a suitable marker for predicting acute MI related future adverse events, and the combination of Killip's class and serum uric acid level after AMI was a good predictor of 30day mortality in patients who have AMI.[5] Ndrepapa *et al* also found that elevated level of serum uric acid was an independent predictor of 1year mortality across the whole spectrum of patients with acute coronary syndromes treated with percutaneous coronary intervention. [10]Our results too showed that SUA significantly correlates with and has a prognostic role in in-hospital and short term (30 days) mortality and occurrence of MACE in patients with ACS, particularly STEMI. SUA can be a useful biomarker for predicting short-term mortality and MACE in this group of patients and can be utilised for early prognosis.

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