UNDERSTANDING THE ROLE OF SERUM URIC ACID AS A PROGNOSTIC MARKER IN ACUTE CORONARY SYNDROME: A HOSPITAL BASED STUDY

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ABSTRACT

BACKGROUND

Coronary artery disease remains the dominating cause of death in the world. Despite understanding and controlling the known risk factors for coronary artery disease, it remains the worldwide epidemic. This raises the possibility of the presence of unknown or underestimated risk factors. The role of uric acid as a prognostic factor in patients with acute coronary syndrome is controversial. The aim of the present study is to estimate serum uric acid levels in acute coronary syndrome and its correlation with Killip's classification of heart failure and in hospital mortality.

MATERIALS AND METHODS

A total of 100 patients with acute coronary syndrome meeting the inclusion and exclusion criteria, with an equal number of age and sex matched controls were selected for study during the period 1st July 2016 - 30th June 2017. Serum uric acid level was estimated on day 0 and 7 of acute coronary syndrome.

RESULTS

A statistically significant higher level of serum uric acid concentration in patients of acute coronary syndrome (5.80 ± 1.53) was observed on the day of admission as compared to controls (3.8 ± 0.85). There was no statistically significant difference observed in relation with diabetes and hypertensive status and gender. Higher serum uric acid (>7 mg/dl) level along with higher Killip's class (III, IV) was associated with higher mortality and major adverse cardiac events.

CONCLUSION

It is concluded from the present study that serum uric acid levels were higher in patients of ACS as compared to healthy controls. Patients with elevated serum uric acid levels belonged to higher Killip's classification and had higher mortality. It can be inferred from this study that serum uric acid can be regarded as an inexpensive independent risk factor and prognostic marker for assessing short term mortality in patients with ACS.

KEYWORDS

Acute Coronary Syndrome, Uric Acid, Killip Class, Mortality.

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BACKGROUND

Cardiovascular disease is responsible for 30% of all deaths in the world. Although the mortality for this condition has gradually declined over the last decades in western countries, it still causes about one-third of all deaths in people older than 35 years. About 80% of the global burden of cardiovascular disease occurs in low and middle-income countries. In India cardiovascular diseases (CVD) have become the leading cause of mortality.[1] CVD affects Indians at least a decade earlier and in their most productive midlife years when compared to the people of European ancestry. India carries a significant portion of this global burden.

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In addition, case fatality attributable to CVD in low-income countries including India appears to be much higher than in middle and high-income countries.[2] Reasons for the high propensity to develop CVD, the high case fatality and the high premature mortality include biological mechanisms, social determinants and their interactions.[3]

Until now various bio-markers have been studied in patients of acute coronary syndrome (ACS). However, no single marker gives definite prognostic information during the course of the disease. While there is no doubt that multiple factors play different roles in the development of acute coronary syndrome, recent studies have revealed the potential role of hyperuricemia as a novel prognostic marker. Uric acid is the final product of purine metabolism in humans, and its level is determined by dietary intake, rate of cell turn-over in the body and renal excretion. Adenosine synthesized locally by vascular smooth muscle in cardiac tissue is rapidly degraded by the endothelium to uric acid, which undergoes rapid efflux to the vascular lumen due to low intracellular pH and negative membrane potential.[4] Under ischemic conditions the activity of xanthine oxidase

and uric acid synthesis are increased in vivo and therefore we can consider elevated serum uric acid as a marker of underlying tissue ischaemia.[5] Epidemiological studies have recently shown that uric acid may be a risk factor for cardiovascular diseases and a negative prognostic marker for mortality in subjects with heart failure and coronary artery disease.

Aims and Objectives

The aim of the present study was to note levels of serum uric acid in acute coronary syndrome, to correlate serum uric acid levels with Killip class and to observe any relationship between serum uric acid level and mortality following acute coronary syndrome.

MATERIALS AND METHODS

The present study was a single centered observational prospective study conducted from July 2016 to June 2017 for a period of one year in the Department of General Medicine at Silchar Medical College and Hospital, Silchar, Assam. A total of 100 patients with acute coronary syndrome meeting the inclusion and exclusion criteria, with an equal number of age and sex matched controls were selected for the study. All patients who were of age greater than 18 years and diagnosed as ACS with at least 2 of the following criteria: a) Presence of typical symptoms like chest pain, palpitation etc on admission b) ECG changes consistent with acute MI in at least 2 contiguous leads c) Elevation of the cardiac enzymes (Troponin T and I, CK-MB) were considered for study. All the patients diagnosed with ACS presented within 12 hours. All acute STEMI patients who presented within 12 hours of onset were eligible for fibrinolytic therapy received fibrinolytic therapy using intravenous streptokinase with the dose of 1.5 million units, and given over 30 to 60 minutes. Patients diagnosed with gout and with other recognized risk factors known to increase serum uric acid levels like renal failure, multiple myeloma, leukaemia, lymphoma, haemolytic anaemia, psoriasis, hypoparathyroidism, chronic alcoholism and patients taking drugs that are known to raise serum uric acid levels like diuretics, chemotherapeutic agents, nicotinic acid, ACE inhibitors like losartan, salicylates, ethambutol and pyrazinamide were excluded from the study.

A detailed history and physical examination with special reference to Killip class was carried out. All patients underwent routine investigations including complete haemogram, renal function tests, liver function tests, ECG, chest x-ray and echocardiography. Patients were followed up till hospital stay i.e. 7 days. Serum uric acid level was measured on day 1 and 7 of ACS.

A detailed statistical analysis was carried out. Basal serum uric acid levels were compared with controls with unpaired 't' test. The levels of serum uric acid on day 1 and 7 were compared by paired 't' test. Uric acid levels and Killip class was compared with coefficient of correlation. The study was approved by the Ethics committee of the hospital.

RESULTS

In the present study, 100 patients with ACS with an equal number of age and sex matched healthy controls were studied. The age of the cases varied from 36 to 85 years, the mean age being 58.13 ± 10.08 years. Maximum number of cases (36%) was in the age group of 50-59 years. Majority of the cases were male (68%) and the male: female ratio was 2.12: 1. In the present study, the highest numbers of patients were non-smoker (67%), and only 33% of patients were smoker. Out of 100 cases, only 7 had family history of IHD as against 2 in the control group. Obesity was found in only 24% of the patients and 36% were overweight. Echocardiogram showed mild LV dysfunction in 32 patients, moderate LV dysfunction in 38 patients, severe in 18 patients and normal LV function in 12 patients. Only 43% of the patients were hypertensive. Type 2 Diabetes mellitus was found in 47% of the patients.

In the present study, majority of the cases were having STEMI (80%), followed by NSTEMI (15%) and Unstable Angina (5%). In the present study the most common presenting symptom was chest pain (92%) followed by increased sweating (52%), nausea and vomiting (28%). Four patients presented with altered mental status.

Mean serum uric acid levels on day 1 was 5.80 ± 1.53 and on day 7 was 4.93 ± 1.26. There is a significant reduction of uric acid levels on Day 7 on comparing with day 0 (P = 0.034). The mean serum uric acid level of controls on day 1 was 3.8 ± 0.85. The baseline characteristics of both the groups are shown in Table 1.

Variables	Cases	Controls	P value
Age (years)	58.13 ± 10.08	58.16 ± 10.18	
Sex (M:F)	68:32	68:32	
Smokers (%)	33	14	0.02
BMI ≥25 (%)	60	54	0.83
Serum uric acid on day 1	5.80 ± 1.53	3.8 ± 0.85	0.001

Table 1. Comparison of Cases and Controls

There was no statistically significant difference in serum uric acid levels when compared with established risk factors like sex, hypertension, diabetes mellitus and smoking in patients with ACS (Table 2).

Parameters			P Value
Hypertension	Yes (43)	No (57)	0.183 (NS)
Serum uric acid	6.03	5.62	
Diabetes mellitus	Yes (47)	No (54)	0.191 (NS)
Serum uric acid	5.07	5.35	
Smoking habit	Yes (33)	No (67)	0.35 (NS)
Serum uric acid	5.31	5.25	
Sex	Male (68)	Female (32)	0.375 (NS)
Serum uric acid	5.28	5.25	

Table 2. Comparison of Serum Uric Acid Levels in Cases with Established Risk Factors

Serum uric acid level on the day of admission was positively correlated with Troponin T levels (Pearson correlation 0.807, P value <0.00001) and CKMB levels (Pearson correlation 0.768, P value <0.00001).

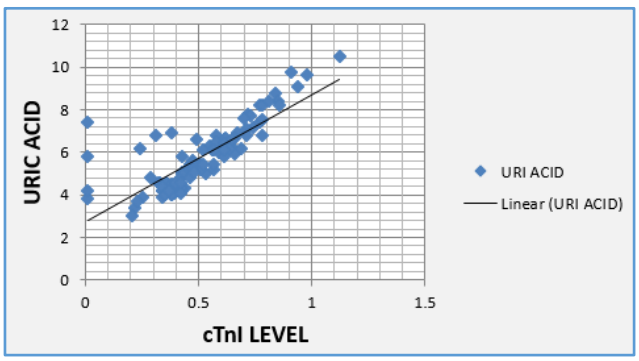

Figure 1. Scatter Plot Depicting Relation between Uric Acid and Troponin t (cTnI)

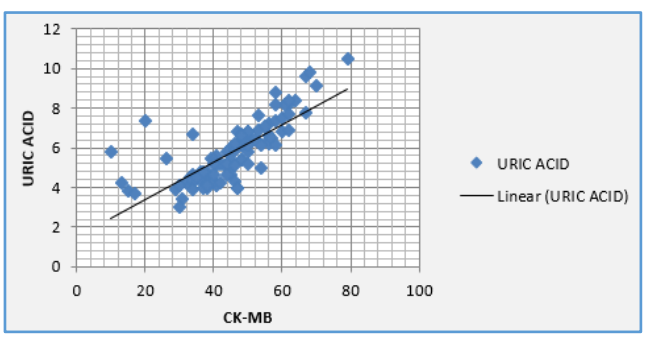

Figure 2. Scatter Plot Depicting Relation between Uric Acid and CK-MB Level

Negative correlation was found between the serum uric acid level on the day of admission and ejection fraction obtained (Pearson correlation -0.827, P value <0.00001).

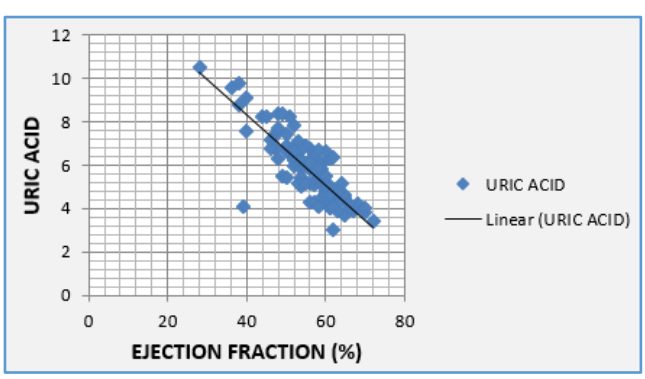

Figure 3: Scatter Plot Depicting Relation between Uric Acid and Ejection Fraction (%)

On day of admission out of 100 patients, 18 patients had serum uric acid >7 mg/dl, in which 14 patients were in Killip class IV and 2 each in class II and III (P value <0.0001).

Killip Classification	Serum Uric Acid <7 mg/dl	Serum Uric Acid >7 mg/dl	Total	P value
I	47	0	47	0.0001
II	15	02	17	
III	17	02	19	
IV	03	14	17	
TOTAL	82	18	100	

Table 3. Correlation of Serum Uric Acid Level with Killip Classification on Day 1

Killip Classification	Serum Uric Acid <7 mg/dl	Serum Uric Acid>7 mg/dl	Total	P value
I	44	00	44	0.05
II	16	00	16	
III	09	03	12	
IV	02	04	06	
TOTAL	71	07	78	

Table 4. Correlation of Serum Uric Acid Level with Killip Classification on Day 7

Mortality	Uric Acid < 7 mg/dl	Uric Acid > 7 mg/dl	Total	P value
DAY 1	2	10	12	0.05
DAY 7	3	7	10	
TOTAL	5	17	22	

Table 5. Correlation between Serum Uric Acid Level and Mortality

Variable	Killip Class i	Killip Class ii	Killip Class iii	Killip Class iv	Total	P value
Day 1	1	0	3	8	12	0.05
Day 7	0	1	3	6	10	
Total	**1**	**1**	**6**	**14**	**22**	

Table 6. Correlation between Killip Class and Mortality

Out of the 22 patients who died, 17 had serum uric acid level > 7.0 mg/dl and 5 patients had serum uric acid < 7 mg/dl. Of these 22 patients, 12 died on the day of admission and 10 patients died over next 7 days. Out of 22 patients who died 14 patients were in Killip class IV.

DISCUSSION

Elevated serum UA levels have been associated with an increased risk for cardio-vascular disease. The potential mechanisms by which serum UA may directly cause cardiovascular risk include enhanced platelet aggregation and inflammatory activation of the endothelium.[6] Previous studies have shown that serum uric acid increases in cardiac failure.[5] In a study done in Japan in 2005 by Kojima et al[7] it was shown that serum uric acid levels correlate with Killip classification. Combination of Killip class and serum uric acid level after AMI is a good predictor of mortality in patients who have AMI.

Present study was conducted in 100 patients of ACS, who presented to hospital with in 12 hrs of onset of symptoms. All the patients with acute STEMI were thrombolysed in our study. One hundred age and sex matched healthy controls were also evaluated for comparison of uric acid levels. Out of 100 patients, 80 had

STEMI, while 15 patients were of NSTEMI and 5 patients had unstable angina.

In the present study, mean age of cases was 58.13 ± 10.08 years and of controls were 58.16 ± 10.18 years. According to study by M Y Nadkar et al[8] the mean age of patients was 58.29 ± 11.31 years and the mean age in control group was 56.84 ± 8.98 years.

Similar findings were also observed in the study conducted by L S Patil et al[9] and Gandiah P et al.[10] There was a statistically significant higher level of serum uric acid concentration in patients with ACS on day of admission as compared to controls (P=<0.00001). This finding of the present study correlated with studies done by Gandiah P et al,[10] M Y Nadkar et al[8], Shirish Agrawal et al.[11]

In the present study there was no significant difference in uric acid levels between male and female patients (P=0.375). Similar finding was observed by, Gandiah P et al[10] and M Y Nadkar et al.[8] However in the study by Kojima S et al[7] males had higher uric acid level as compared to females.

There was no significant difference in uric acid levels between hypertensive and non-hypertensive patients (P=0.183). This finding of the present study correlated well with the studies by L S Patil et al,[9] M Y Nadkar et al,[8] Qureshi et al.[12] In contrast to finding of present series Harris P et al[13] and Kojima S, et al[7] noted that serum uric acid level was significantly correlated with hypertension. In another study by Chen L et al[14] serum uric acid was significantly associated with hypertension in patients aged <40 years.

There was no significant difference in uric acid levels between diabetic and non-diabetic patients (P= 0.1910). This finding was in concordance with the study by L S Patil et al,[9] M Y Nadkar et al 8 and Toumilheto et al[15] in which there was no significant association between serum uric acid and diabetic status. However, this finding is in contrast to other study by Safi et al,[16] and Harris P et al[13] where hyperuricemia was significantly associated with type 2 diabetes mellitus. There was no significant difference in uric acid levels between smokers and non-smokers which was similar to the study by Qureshi et al.[12]

Serum uric acid level on the day of admission was correlated with Troponin T value. A strong positive correlation was obtained (Pearson correlation 0.807, P value <0.00001), that is, as the value of one increases the other also increases. Hasic et al[17] in their study found the similar positive correlation. In the study of Lippi et al[18] significantly higher serum UA levels in patients with Troponin T values above decisional threshold was revealed.

Serum uric acid level on the day of admission was correlated with CK-MB value. A strong positive correlation was obtained (Pearson correlation 0.768, p value <0.00001). Similarly, Amrut A Dambal et al[19] and Harris P et al[13] also found statistically significant positive correlation between CK-MB and uric acid on day of admission.

In the present study when serum uric acid level on the day of admission was correlated with ejection fraction (%). A strong negative correlation was obtained (Pearson correlation -0.827, p value <0.00001). Chen L et al[14] showed a significantly lower LVEF in patients with high serum uric acid. Yoshiro et al[20] and Pinelli M, et al[21] clarified in their study that high UA levels reduced LVEF independently of the severity of ischemic heart disease (IHD). In contrast Nozari Y et al[22] there was no correlation between uric acid and LVEF (Correlation coefficient= -0.111, p =0.129).

In the present study, out of 100 patients, 18 patients had serum uric acid >7 mg/dl, in which 14 patients were in Killip class IV and 2 each in class II and III (p value <0.0001, highly significant). Thus, patients of Killip class IV had higher levels of uric acid as compared to other Killip classes. In a study done in Japan in 2005 by Kojima S et al[7] it was shown that serum uric acid levels correlate with Killip classification. M Y Nadkar et al[8] also found that there was a positive correlation between serum uric acid level and Killip class on day of admission. Similar findings were also observed by L S Patil et al[9] and Gandiah P et al.[10]

In the present study, there was significant correlation between uric acid level and in-hospital mortality. High serum uric acid levels on admission were strongly associated with increased mortality. In the present study out of 100 cases, 22 patients (22%) died. More than half of the patients (12) died on the day of admission and 10 patients died over next 7 days. Out of the 22 patients who died, 17 had serum uric acid level more than 7.0 mg/dl and 5 patients had serum uric acid less than 7.0 mg/dl.

Bickel C et al[23] reported that one mg/dl increase in serum uric acid levels was associated with a 26% increase in mortality. Siniša Carl et al[24] and M Y Nadkar et al[8] concluded in their study that serum uric acid level after acute myocardial infarction is a good predictor of mortality.

Out of 12 patients died on the day of admission (day 1), 8 patients were in Killip class IV, 3 patients in Killip class III and 1 patient in Killip class I. Over next 7 days another 10 patients died, out of which 6 were in Killip class IV, 3 in Killip class III and 1 in Killip class II. In the study by M Y Nadkar et al 8 83% of patients who died were in higher class i.e. class III and IV at time of admission. Similar observations were found in the study by by L S Patil et al[9] and Gandiah P et al.[10]

CONCLUSION

It is concluded from the present study that serum uric acid levels were higher in patients of ACS as compared to healthy controls. Patients with elevated serum uric acid levels belonged to higher Killip's classification and had higher mortality. It can be inferred from this study that serum uric acid can be regarded as an inexpensive independent risk factor and prognostic marker for assessing short term mortality in patients with ACS.

Although, conduction of this study in a sole institution with paucity of time and resource highlighted the role of serum uric acid in influencing the course of ACS, a more elaborate multi centric study would have been desirable to precisely establish the role of serum uric acid in ACS. It is hoped that the present study will encourage new studies related to the above subject with a broader spectrum and for longer durations.

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