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Original Research Article

A comparative study of serum uric acid level in various acute coronary syndromes and its short term prognostic significance using KILLIP classification

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ABSTRACT

Background: Serum uric acid is increased in ischemic conditions and is significantly higher in patients with acute myocardial infarction. The aim of study was to correlate serum uric acid level with KILLIP class in respect of mortality and morbidity profile of patients with acute coronary syndromes..
Methods: 100 patients fulfilling the standard diagnostic criteria for acute coronary syndromes on the basis of classical history, clinical signs, ECG changes and biomarkers were included in the study. Age and sex matched 50 normal healthy subjects were also included as control group after obtaining informed consent. Serum uric acid level was measured on day 0, 3 and 7 of various ACS.
Results: There was statistically significant higher level of serum uric acid concentration in patients of AMI on day of admission as compared to controls and unstable angina patients. On all three days of serum uric acid estimation, the serum uric acid levels were higher in AMI patients who were in higher KILLIP class as compared to lower KILLIP class group. Smokers had significantly higher baseline serum uric acid but age, sex, dyslipidemia, hypertension and diabetes mellitus did not significantly affect serum uric acid level at any stage in various ACS patients. Five patients who died during hospital stay, had serum uric acid level more than 7.0 mg/dL and all of them were in KILLIP class III and IV.
Conclusions: serum uric acid level is a strong and independent risk factor in predicting mortality and morbidity profile of patients of acute myocardial infarction. Also, serum uric acid level correlates well with KILLIP class.

Keywords: Acute coronary syndromes, KILLIP class, Serum uric acid

INTRODUCTION

Acute myocardial infarction is the leading cause of mortality and morbidity in present days. Following acute MI , cardiac markers such as proteins (myoglobin) and enzymes (CK MB, Troponin T) are released into blood stream from necrotic heart muscle and have a characteristic temporal characteristic profile . However they do not correlate with the mortality and morbidity profile following AMI. There are several newer markers in ischemic heart disease like hs-CRP, lipoprotein a, plasma fibrinogen, antithrombin III, homocysteine etc. All of them are relatively costlier and their prognostic significance is doubtful. As compared to them serum uric acid level estimation is much cheaper easily available and also it can have prognostic value post myocardial infarction.

Epidemiological studies have recently shown that serum uric acid may be an independent risk factor for cardiovascular disease and a negative prognostic marker for mortality and morbidity in subjects with pre-existing heart failure.[1-3] National health and nutrition examination survey 1 [NHANES 1] has convincingly established the role of serum uric acid as an independent predictor of cardiovascular mortality in subjects older than 45 year regardless of sex, race, menopausal status, diuretics use and presence of cardiovascular disease.

Pathophysiological studies show that serum uric acid level increases in ischemia via adenosine pathway catalyzed by xanthine oxidase. Adenosine synthesized locally by vascular smooth muscle in cardiac tissue, is rapidly degraded by endothelium to uric acid, which undergoes rapid efflux to the vascular lumen due to low pH, and negative membrane potential.[4]

Uric acid and xanthine oxidase levels are increased in vivo under ischemic conditions and hence serum uric acid acts as a marker of underlying ischemic conditions.[5] Hyperuricemia is associated with deleterious effects on endothelium dysfunction, oxidative metabolism, platelet adhesiveness hemorheology and aggregation. There is evidence that high serum uric acid is a negative prognostic factor in patients with mild to severe heart failure.[6] According to a recent study done in Japan there was close correlation between serum uric acid concentration and KILLIP classification in patients of acute myocardial infarction. Patients who developed short term adverse events had high serum uric acid concentrations.[7]

In this study we planned to note the levels of serum uric acid in various acute coronary syndromes, to correlate serum uric acid levels with KILLIP class and to note relationship between serum uric acid level and mortality and morbidity profile of the patient following acute coronary syndromes.

METHODS

100 patients fulfilling the standard diagnostic criteria for acute coronary syndromes namely ST segment elevated MI, Non ST segment elevated MI and unstable angina on the basis of classical history, clinical signs, ECG changes and biomarkers (Troponin T and I, CPK-MB) were included in the study.

Age and sex matched 50 normal healthy subjects were also included as control group after obtaining informed consent. Any patient with a condition known to elevate uric acid level e.g. chronic kidney disease, gout, hematological malignancy, hypothyroidism etc. were excluded. Also, patients on drugs which increase serum uric acid e.g. Salicylates (>2 gm/d), diuretics, ethambutol, pyrazinamide etc. and also chronic alcoholics were excluded.

A detailed history and physical examination with special reference to KILLIP class was carried out. All patients underwent routine investigations including Hb, CBC, renal function tests, liver function tests, lipid profile ECG, chest x-ray. Patients were followed up till for a minimum period of 7 days in hospital stay. Serum uric acid level was measured on day 0, 3 and 7 of ACS.

Statistical analysis

The result were expressed as mean±SD of each variable. The comparison between means was performed by student t test and ANOVA test. P-value of 0.05 or less was interpreted as significant for the analysis.

RESULTS

We studied 100 patients with acute coronary syndromes and 50 age and sex matched healthy controls. There was no significant difference in age and sex distribution. But, serum uric acid level on day 0 showed significant difference (p value <0.05) in patients (mean serum uric acid on day 0 = 6.44±2.06 mg/dl) and controls (mean serum uric acid on day 0 = 4.22±0.52 mg/dl) group. Patients group had higher mean serum uric acid level as compared to control group (Table 1).

Table 1: Comparison of patients and controls.

	Patients (n=100)	Control (n=50)	P value
Age (years)	56.25±12.8	54.15±9.8	NS (not significant)
Sex M/F	70:30	32:18	NS (not significant)
S. Uric acid Day 0 (mg/dl)	6.44±2.06	4.22±0.52	<0.028 (significant)

Table 1 shows comparison between patients and controls (n=50) group according to age and sex distribution and serum uric acid level on day 0.

There was no significant(p value >0.05) increase in mean serum uric acid levels in patients who had hypertension, diabetes and dyslipidemia as risk factors as compared to patients who did not have them irrespective to category of acute coronary syndrome.

Patients with history of smoking had significantly (p value <0.05) higher serum uric acid level as compared to non-smokers on day 0 in various acute coronary syndromes. However further detailed controlled study may be required to clarify this (Table 2).

Table 2 shows that there is significant rise in mean serum uric acid level in patients who smoked as compared to patients with other risk factors namely DM, hypertension, and dyslipidemia.

Patients in KILLIP class IV had higher serum uric acid level as compared to class I, II and III on day 0, day 3 and day 7. Patients in KILLIP class III had higher serum uric acid level than class I and II on day 0, day 3 and day 7.

Patients in KILLIP class II had higher serum uric acid level than class I on day 0, day 3 and day 7. Therefore there is significant (p value <0.001) correlation between KILLIP class and serum uric acid level which shows that higher the KILLIP class is, higher is the level of serum uric acid (Table 3).

Table 2: Comparison of serum uric acid on day 0 with respect to risk factors in total number of patients.

		Number of patients	Uric acid on day 0 (Mean±SD) mg/dl	p-value
Hypertension	Present	55	6.40±2.28	0.319(not significant)
	Absent	45	6.84±2.14	
DM	Present	31	6.39±1.93	0.51(not significant)
	Absent	69	6.69±2.34	
Smoking	Present	53	7.01±2.10	0.048(significant
	Absent	47	6.13±2.28	
Dyslipidemia	Present	22	6.35±2.35	0.611(not significant)
	Absent	77	6.65±2.14	

Table 3: Comparison of serum uric acid level at baseline/day 0, at 3rd day, 7th day and KILLIP's class.

	KILLIP'S class				p-value
	I	II	III	IV	
Number of patients	40	30	16	14	
Uric acid Baseline/day 0 (mg/dl)	4.57±1.23	7.10±0.87	8.39±1.38	9.27±2.01	<0.001 (significant)
Number of patients	40	30	15	12	
Uric acid at 3rd day(mg/dl)	4.54±1.07	6.75±1.07	7.61±0.68	9.07±1.63	<0.001 (significant)
Number of patients	40	30	15	10	
Uric acid at 7th day(mg/dl)	4.21±1.00	6.32±1.57	7.22±0.67	8.33±1.56	<0.001 (significant)

Table 4: Comparison of serum uric acid level at baseline, at 3rd day, 7th day and various acute coronary syndromes.

Uric acid at (in mg/dl)	Acute coronary syndromes			P-Value
	STEMI	NSTEMI	UA	
Baseline /day 0	7.26±2.11	6.76±1.69	3.80±1.12	<0.001 (significant)
3rd day	6.75±1.90	6.51±1.52	4.02±1.11	<0.001 (significant)
7th day	6.15±1.88	6.17±1.67	3.82±1.14	<0.001 (significant)

Table 3 shows that there is statistically significant rise in mean serum uric acid level as the KILLIP'S class progressed from I to IV (p value <0.001).

Comparison was also done to see any co-relation between serum uric acid level and various acute coronary syndrome patients. STEMI patients had higher serum uric acid levels on day 0, day 3 and day 7 as compared to NSTEMI and unstable angina patients. There was significantly higher (p <0.001) serum uric acid level in STEMI patients as compared to unstable angina patients on day 0, day 3 and day 7 and similar difference were found between NSTEMI and unstable angina. Although STEMI patients had higher serum uric acid level as compared to NSTEMI patients but the difference found in serum uric acid level between STEMI and NSTEMI was not statistically significant. All the five patients who died during hospital stay, had serum uric acid level more than 7.0 mg/dl and all of them were in KILLIP class III and IV (Table 4).

Table 4 shows that STEMI patients had higher serum uric acid levels on day 0, day 3 and day 7 as compared to NSTEMI and unstable angina patients.

DISCUSSION

Previous studies have shown that serum uric acid level increases in cardiac failure.[5] In a study done in Japan in 2005 by Kojima et al, it was shown that serum uric acid levels correlate well with KILLIP class.[7] Combination of KILLIP class and serum uric acid level after acute myocardial infarction is a good predictor of mortality in patients who have acute myocardial infarction. Our study

was carried out in 100 patient of various acute coronary syndromes admitted in the medical wards of MBS hospital, Kota. Fifty, age and sex matched healthy controls were also evaluated for comparison of serum uric acid level. The patients were divided into three groups: ST elevated MI, non ST elevated MI and unstable angina on the basis of clinical, ECG and laboratory characteristics as per standard criteria for diagnosing various acute coronary syndromes. Out of total 100 patients, 56 patients had ST elevated MI, 29 patients had non ST elevated MI and 15 patients were diagnosed with unstable angina. The patients were selected over a period of one year. Serum uric acid was treated as a continuous variable and as a categorical variable, and variables were divided into quartiles according to serum uric acid concentrations same as in referral study by Kojima et al.[7]

In study group of 100 patients mean age was 56.25 yrs. with standard deviation of 12.8 with mean serum uric acid level(6.44±2.06 mg/dl).The mean age in control group was 54.15yrs with standard deviation of 9.8 and mean serum uric acid level was (4.22±0.52 mg/dl) (Table 1). So in our study , patients had higher mean serum uric acid level as compare to control group (p value <0.028). There was no correlation (p value=0.121) between serum uric acid level on admission and different study age groups in our study and study by Kojima et al, as well. In our study there was no significant (p value=0.757) difference between serum uric acid levels on admission and different sex groups. However, in study by Kojima S et al, males had higher serum uric acid levels as compared to female.[7] Nadkar MY also showed no correlation between serum uric acid level and different sex group.[8] Out of 100 patients, 55% (n=55) patients were hypertensive in our study. We did not find any significant correlation (p value = 0.319) between serum uric acid level and status of blood pressure (hypertensive or normotensive). This is similar to the study by Nadkar MY.[8] However some studies have shown positive correlation between serum uric acid level and status of hypertension.[7]

There were 31 out of 100 patients who were diabetics. So in our study we did not find any significant correlation (p value = 0.51) between serum uric acid level and diabetes mellitus. So this finding is consistent with study by Tuomilheto et al, and Nadkar MY study.[8,9] However, some study studies have shown positive correlation between serum uric acid level and type 2 diabetes mellitus.[10] We also compared mean serum uric acid level on day 0, day 3 and day 7 in different acute coronary syndrome (STEMI, NSTEMI and Unstable angina) patients with and without diabetes.

In this study 22 patients out of 100 were found to have some form of dyslipidemia primarily high total cholesterol, high LDL and high triglycerides diagnosed as per standard criteria either alone or in combination. We found no significant (p value=0.611) correlation between serum uric acid level and dyslipidemia.

The 53 patients out of 100 were smokers. In our study we found significant correlation (p value=0.048) between mean serum uric acid level on admission with respect to history of smoking. However further detailed controlled study may be required in future to clarify this.

On the basis of clinical, ECG and laboratory characteristics patients were divided into three groups ST elevated MI, non ST elevated MI and Unstable angina.

Serum uric acid level was measured in all 100 patients on the day of admission (day 0), on day 3 and on day 7. Patients with ST elevated MI had serum uric acid level (7.26±2.11 mg/dl), (6.75±1.90 mg/dl), (6.15±1.88 mg/dl) on day 0, day 3 and day 7 respectively. Patients with non ST elevated MI had serum uric acid level (6.76±1.69 mg/dl), (6.51±1.52 mg/dl), (6.17±1.67 mg/dl) on day 0, day 3 and day 7 respectively. Patients with unstable angina had serum uric acid level (3.80±1.12 mg/dl), (4.02±1.11 mg/dl), (3.82±1.14 mg/dl) on day 0, day 3 and day 7 respectively.

STEMI patients had higher serum uric acid levels on day 0, day 3 and day 7 as compared to NSTEMI and unstable angina patients. There was significant higher (p <0.001) serum uric acid level in STEMI patients as compared to unstable angina patients on day 0, day 3 and day 7 and similar difference was found between NSTEMI and unstable angina. Mean serum uric acid level on day 0 in patients of unstable angina (3.80±1.12 mg/dl) was not significantly higher when compared to normal healthy controls (4.22±0.22mg/dl). Although STEMI patients had higher serum uric acid level as compared to NSTEMI patients but the difference found in serum uric acid level between STEMI and NSTEMI was not statistically significant. However in referral studies by Nadkar MY[8] et al and Kojima et al[7] showed higher serum uric acid level in acute MI patients but there were no significant difference between STEMI and NSTEMI patients.

There was correlation between serum uric acid level and KILLIP class in acute myocardial infarction as in earlier studies by Nadkar MY et al[8] and Kojima et al.[7] Previous studies have shown that serum uric acid level increases in cardiac failure.[11,12]

In our study serum uric acid levels correlate with severity of cardiac failure as per KILLIP class. Patients in KILLIP class IV had significantly (p value <0.001) higher serum uric acid level (9.27±2.01 mg/dl), (9.07±1.63 mg/dl), (8.33±1.56 mg/dl) on day 0, day 3 and day 7 respectively as compared to class III (8.39±1.38 mg/dl), (7.61±0.68 mg/dl), (7.22±0.67 mg/dl), class II (7.10±0.87 mg/dl), (6.75±1.07 mg/dl), (6.32±1.57 mg/dl) and class I (4.57±1.23 mg/dl), (4.54±1.07 mg/dl), (4.21±1.00 mg/dl). This finding is consistent with referral studies.[7,8] Hence serum uric acid can be used as prognostic indicator in management of patients with acute myocardial infarction.

Out of 100 patients, 5 died during 7 day follow up, of which 3 were male and 2 were female. All patients who died during this period had serum uric acid level more than 7 mg/dl. Out of 5 patients 1 was in KILLIP class III and 4 were in KILLIP class IV at the time of admission. There was a rising trend of serum uric acid level before they died during 7 day follow up. It shows that serum uric acid concentration is significantly correlated with mortality and morbidity profile of patients after acute myocardial infarction.

CONCLUSION

As compared to normal healthy control group, patients suffering from acute myocardial infarction (STEMI and NSTEMI) had significantly higher serum uric acid level at the time of hospital admission. However there was no significant difference found in serum uric acid level in patients of unstable angina and normal healthy controls. There was significant correlation between serum uric acid level and various KILLIP class in patients of acute myocardial infarction. It was found that significantly higher serum uric acid level was present, as the KILLIP class progressed from class I to class IV. When comparison was done amongst various acute coronary syndrome patients, it was found that patients suffering from acute myocardial infarction (STEMI and NSTEMI) had significantly higher serum uric acid level as compared to patients suffering from unstable angina. In this study, it was found that status of age, sex, dyslipidemia, hypertension and diabetes mellitus did not significantly affect serum uric acid level in various acute coronary syndrome patients .However when comparison was made between smokers and non-smokers, it was found that patients of various acute coronary syndromes who were smoker had significantly higher serum uric acid as compared to non-smoker. In this study, the patients who died during hospital stay belonged to higher KILLIP class groups (class III and IV) and had significantly higher serum uric acid level when compared to lower KILLIP class patients group. Hence it is concluded that serum uric acid level was a strong and independent risk factor having significant prognostic value in predicting the mortality and morbidity profile of patients following acute myocardial infarction.

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