Study of Serum Uric Acid Levels in Myocardial Infarction and Its Association With Killip Class

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Abstract- The present study aimed to compare the serum level of uric acid in patients with and without heart failure and also to determine the association between uric acid level and clinical status by Killip class in patients with STEMI. This case-control study was conducted on 50 consecutives as control group and 50 patients with acute heart failure, (20 patients had acute STEMI), who documented by both clinical conditions and echocardiography assessment. The mean plasma level of uric acid in the case group was 7.6±1.6 milligrams/deciliter (mg/dL) and in the control group was 4.5±1.5 respectively (P<0.001). These values in patients with STEMI was about 9.2±0.86, but in patients with acute heart failure in absence of STEMI was 6.5±1.04 (P<0.001). Moreover, there was significant difference among the level of uric acid and Killip classes (P<0.001). Also there was significant difference for uric acid level between HFrEF (HF with reduced EF) and severe LV systolic dysfunction (0.049). In STEMI patients with culprit LAD, mean uric acid was significantly higher than cases with culprit LCX [(9.7±0.98 versus 8.6±0.52 respectively) P=0.012]. Regarding treatment plan in patients with STEMI, mean level of uric acid in those considered for CABG was significantly higher than who were considered for PCI, 9.9±0.82 versus 8.9±0.76 respectively, P=0.029. In STEMI patients with higher killip class, higher level of uric acid was seen. Also, the severity of LV systolic dysfunction was associated with higher level of uric acid.

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Keywords: Heart failure; Uric acid; Killip class; Myocardial infarction

Introduction

Uric acid is a metabolite of purines (1). Hyperuricemia is generally defined as serum uric acid at least 6 mg/dL in women and at least 7 mg/dL in men (2-4). It has been shown that uric acid induces endothelial dysfunction by activating the HMGB1/RAGE signaling Pathway (5).

The researchers identified uric acid as a predictor also an independent risk factor for coronary heart disease (6). It also used as a biomarker for inflammation (1).

In recent issues of published research reports, the elevation of uric acid has been introduced as a major prognostic marker predicting mortality as well as the need for heart transplantation in patients with progressive heart failure (7,8). In fact, the assessment of this biomarker alone or in combination with other parameters of cardiac function and clinical status has been suggested to be hopeful for appropriately managing the patients in future (9). Some pathophysiological processes have been identified explaining the association between the production and metabolism of uric acid and progression and outcome of heart failure (10). One of these mechanisms includes the activity of xanthine oxidase pathway resulting deterioration of left ventricular function via changing calcium sensitivity of myofilaments as well as by interfering with myocardial energetic pathway (11). Regardless of the meditative role of xanthine oxidase

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pathway, uric acid itself may a certain role in cardiovascular and renal dysfunction through stimulating vascular smooth muscle cell proliferation leading renal vascular disease, renal disease, systemic hypertension, and hemodynamic instability (12,13). Also, the role of hyperuricemia on endothelial function in the human vascular bed has been shown (14). Thus, the increase in serum level of uric acid can be a valuable indicator for progression of heart failure lead to poorer patients' outcome and reducing their long-term survival. However, the effect of hyperuricemia in acute heart failure due to myocardial infarction has not been well understood. The present study aimed to compare the serum level of uric acid in patients with and without heart failure and also to determine the association between hyperuricemia and the Killip class (15), after myocardial infarction in patients with heart failure.

Materials and Methods

This case-control study was conducted on 100 participants. Fifty patients were selected as case group who had been hospitalized with acute heart failure due to acute myocardial infarction or without acute myocardial infarction but documented by both clinical condition and echocardiography assessment.

Fifteen healthy subjects, who had been visited at the same time for routine cardiology checkup, were also enrolled as normal control group. They hadn't history of cardiovascular problems and they had normal echocardiography.

Among cases, twenty patients were hospitalized due to acute ST-segment elevation myocardial infarction (STEM). All type of STEMI was randomly selected.

Those with the recent use of diuretics or every drug effective on uric acid metabolism, history of gout, hematological malignancy, chronic alcoholics, hypothyroidism, renal disorders, were all excluded from the study.

Blood samples were taken for measurement of complete blood count, differential count, creatinine, and cardiac troponin, uric acid, lipid profile, and glucose at the critical care unit during 1 hour after presentation. In patients with STEMI, Killip classification used as a functional status also an indicator of severity of heart failure (15-17). Troponin I more than 0.11 ng/ml was considered as a positive value and was applied for documentation of STEMI.

Baseline characteristics and clinical data of participants were collected by patients' interviewing and recorded at study checklists.

All subjects underwent two-dimensional echocardiography to determine left ventricular ejection fraction (LVEF) and left ventricular diastolic function.

We categorized our patient's on basis of defined LVEF in echocardiography. Those with LVEF≥50% were considered as a heart failure with preserved (HFpEF), Patients with an LVEF in the range of 40–49% were considered as a HF with midrange or HFmrEF and those with LVEF less than 40%; were defined as a HF with reduced EF (HFrEF).For better discrimination, we also select the patients who had LVEF≤30 % as a separate group with severe LV systolic dysfunction (18).

Except 10 patients with previous documented diagnosis of non-ischemic dilated cardiomyopathy, all of the cases underwent coronary angiography to assess the presence and severity and patterns of coronary artery involvement. The concentration of uric acid was measured by a method of uric acid enzyme and enzymatic peroxides.

Results were presented as mean±standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Quantitative variables were also compared with t test and ANOVA. For the statistical analysis, the statistical software SPSS version 18.0 for windows (SPSS Inc., Chicago, IL) was used. *P*.values of 0.05 or less was considered statistically significant.

Results

Sex distribution of case group was 22 female (44%) and 28 male (56%). Control group was comprised of 21 female (42 %) and 29 male (58 %) (*P*.value=0.8). The mean age of case group was 55.06±8.5 years and 55.6±9.5 in control group (*P*.value=0.7).

In cases, 20 (40 %) patients and in control group, 15(30 %) subjects had systemic hypertension. Sixteen patients (32 %) in cases and 15 (30 %) in controls had history of documented diabetes mellitus type II. Thirty nine (78 %) in case group and 35 cases in control group (70%) were smokers, too. Hypertriglyceridemia (more than 150 mg/dl) was detected in 13 (26 %) of cases and in 15 (30 %) of controls.

Hypercholesterolemia (more than 200 mg/dl) were seen in 19 (38 %) of cases and in 12 (24 %) of subjects in control group.

The mean plasma level of uric acid in the case group was 7.6±1.6 milligrams/deciliter (mg/dL) and in the control group was 4.5±1.5 respectively (*P*<0.001).

These values in patients with STEMI was about 9.2±0.86, but in patients with acute heart failure in absence of STEMI was 6.5±1.04 (*P*<0.001).

In 20 patients with STEMI, there were 5 patients in Killip class I, 8 patients in Killip classes II, 4 patients in Killip classes III and 3 patients in Killip class IV. Mean uric acid levels was 8.2±0.19 mg/dl in the group with Killip class I, 9.02±0.34 mg/dl in the group with Killip class II, and 9.91±0.23 mg/dl in those with Killip III and 10.59±0.28 in patients with Killip class IV (*P*<0.001).Post hoc analysis showed significant *P*.value (0.001) for uric acid level just between Killip class I and IV .There weren't *P*.value<0.05 in comparison among other Killip classes.

In case group, regarding level of uric acid and LV systolic dysfunction we got these results. The uric acid level was 8.8±0.15 mg/dL in 2 cases (4%) with preserved LV Systolic function, 8.7±0.53 mg/dL in 8 patients(16%) with HFmrEF, 6.8±1.7 mg/dL in 21 cases (42%) with HFrEF and 7.8±1.6 mg/dL in 19 cases (38%) with severe LV Systolic dysfunction (*P*=0.017). In Post hoc analysis there was significant *P*.value for uric acid level between HFrEF and severe LV systolic dysfunction (0.049). There weren't *P*.value<0.05 in comparison among other LV systolic dysfunctions. Analysis of diastolic dysfunction showed there weren't any relationship among type of LV diastolic dysfunction and mean plasma uric acid level (*P*=0.3) (Table 1).

Table 1. The mean uric acid levels for diastolic dysfunction in cases group

Grade of diastolic dysfunction	Number of patients		Uric acid level	
Subscales	**n**	**%**	**M**	**SD**
I	8	16 %	8.4	1.8
II	22	44%	7.5	1.7
III	13	26%	7.1	1.6
IV	7	14 %	7.6	0.35

For culprit artery in angiography of STEMI patients, left anterior descending artery (LAD) was involved in 7 patients with mean uric acid level of 9.7±0.98, Left circumflex artery (LCX) was responsible in 6 patients with uric acid level of 8.6±0.52 and in cases with culprit right coronary artery (RCA), with mean uric acid level of 9.2±0.64 (*P*=0.04). In post hoc analysis, significant values was seen just between cases with culprit LAD and culprit LCX (*P*=0.012).

Moreover, there weren't significant difference among the level of uric acid and treatment plan of all cases including those with STEMI or those without STEMI (*P*=0.2) (Table 2).

Table 2.The mean uric acid levels regarding treatment plan in total of cases group

Treatment plan	Number of patients		Uric acid level	
Subscales	**n**	**%**	**M**	**SD**
Medical Therapy	25	50	7.2	1.1
PCI	13	26	8.1	1.5
CABG	12	24	7.7	2.4

Also, there wasn't significant difference between the level of uric acid and treatment plan in patients with STEMI (*P*=0.055), but in post hoc analysis, mean plasma level of uric acid in those considered for coronary artery bypass grafting (CABG) was significantly higher than who were considered for Percutaneous coronary intervention (PCI), 9.9±0.82 versus 8.9±0.76 respectively, *P*=0.029. Also these values weren't significant in who were considered for medical therapy (8.7±0.68) versus PCI (*P*=0.68) or versus CABG (*P*=0.052). Among cases with heart failure in absence of STEMI, regarding treatment plan, there was significance difference (*P*=0.01) among uric acid level for medical therapy, PCI and CABG (Table 3).

Table 3. The mean uric acid levels regarding treatment plan in cases group in absence of STEMI

Treatment plan	Number of patients		Uric acid level	
Subscales	**n**	**%**	**M**	**SD**
Medical therapy	20	66.7	6.8	9.2
PCI	4	13.3	6.1	0.86
CABG	6	20	5.5	0.94

Discussion

The present study could well show a remarkably higher level of uric acid in patients with heart failure (cases group) in comparison with controls group.

Moreover, in patients with STEMI, the level of uric acid was significantly higher than patients with heart failure in absence of STEMI. The main finding of our study was that the upper the Killip class, the higher the uric acid level. It shows that uric acid could be a indicator for worse clinical outcome in STEMI patients.

More interestingly, the level of this biomarker was significantly associated with severity of LV systolic dysfunction; particularly in patients with severe LV systolic dysfunction, it was significantly higher than patients with HFrEF.

Our work was consistent with previous studies which showed hyperuricemia was common in patients with HF. Several studies have shown association of elevated uric acid with heart failure. Elevated uric acid level was independently associated with long term poor outcomes in these patients (19). One study showed significant correlation between uric acid level and some established prognostic markers in patients with chronic heart failure (CHF). They suggest that uric acid can be measured anywhere at a low cost to select high-risk patients with CHF (20).

In a recent study by Okazaki H *et al.*, the patients with severely decompensated acute heart failure (AHF), were divided into a low uric acid group (UA≤7.0 mg/dl) or a high uric acid group (UA>7.0 mg/dl) according to their uric acid level on admission. In patients who were hospitalized during an emergent condition for AHF, uric acid was an independent predictor. High serum uric acid on admission was associated with the presence of chronic kidney disease and the use of loop diuretics. In hyperuricemic patients with AHF, these factors were also correlated with adverse outcomes (21).

According to a direct association between plasma level of uric acid and progression of heart failure, it seems that hyperuricemia may be a valuable indicator for poor outcome in heart failure patients. In a recent systematic review, it was shown that increased risk of incident heart failure can be associated with hyperuricemia and also cardiovascular mortality, composite of death or cardiac events and risk of all other mortality cause. In this regard, for every 1 mg/dL increase in serum uric acid, the odds of development of heart failure increased by 19% and the risk of total mortality and the combined endpoint in patients with heart failure increased by 4% (22).

Regarding association between uric acid level and STEMI, our findings as stated previously, confirmed results of previous studies. In one case control study, in patients with acute myocardial infarction (AMI), serum uric acid level on day of admission, was significantly higher than control group. In cases that were in higher Killip class, Serum uric acid levels were higher. All the five died patients with Killip class IV, had only three days of hospitalization and their serum uric acid was elevated more than 7.0 gm/dL (23).

Akpek M and his colleagues, studied association of serum uric acid levels on coronary flow in patients undergoing primary PCI. They showed among patients with STEMI, Plasma uric acid level on admission was an independent and powerful predictor of poor coronary blood flow after primary PCI, also in hospital major adverse cardiac events (6).

In a similar work, Patients with higher serum uric acid levels were in higher Killip category, and more elevated uric acid were associated with higher mortality (24).

Results of a recent study on correlation of serum uric acid with prognosis in AMI showed, in Patients with Killip class lll and lV, higher levels of uric acid were detected as compared to patients with class l and ll. They suggested, sum of serum uric acid level and Killip class is a good predictor of severity of heart failure after acute myocardial infarction (25).

A published meta-analysis in 2014 identified, uric acid level was a strong prognostic factor for in-hospital mortality in patients with AMI (26).

According to a newest study in this regard, they mentioned hyperuricemia associated with increased the one year mortality of STEMI patients just in Killip class I. In their view, An interaction and correlation of hyperuricemia and Killip class can dramatically affects

the mortality of Patients with STEMI (1).Unfortunately, we didn't consider prognosis or mortality of patients in our study.

Recent articles have paid attention to relationship between serum level of uric acid and severity of coronary artery disease (CAD) (27,28). In our study, as mentioned previously, we could show higher uric acid level in culprit LAD versus culprit RCA, but we didn't calculate coronary angiographic score like syntax score.

According to study findings, in STEMI patients with higher killip class, higher levels of uric acid are seen. Also, the severity of LV systolic dysfunction could be associated with higher level of uric acid. Therefore, uric acid may be considered as a practical and useful biomarker for risk stratification of patients with STEMI. Moreover, targeting involved enzymatic pathway in uric acid cycle can be a therapeutic goal in these settings.

Large-scale randomized clinical trials are needed to evaluate uric acid for this above mentioned purposes.

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