HIGH SERUM URIC ACID LEVELS AS A MARKER OF POOR CARDIOVASCULAR OUTCOME AND HIGH MORTALITY

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ABSTRACT

Objective: *To access the correlation of high serum uric acid with cardiovascular morbidity and mortality in patients having Congestive heart failure (CHF).*

Material and Methods: *This descriptive cross sectional study was performed in Department of Medicine Fauji Foundation Hospital Rawalpindi. Serum uric acid was measured in 66 patients with CHF diagnosed on the basis of an ejection fraction < 50%. Patients were prospectively followed during a median follow-up period of 30 days with end points of cardiac death or rehospitalization. Out of 66 patients, 6 patients were lost to follow up at some stage of data collection and were excluded.*

Results: *Out of 60 patients finally analyzed, 25 (41.7%) patients had normal uric acid and 35 (58.3%) patients had high uric acid. More patients with high uric acid levels were in severe heart failure as compared to those with normal uric acid levels (p= 0.00). Patients with high uric acid levels had more deaths (p= 0.484). Patients with higher uric acid levels required significantly more rehospitalization as compared to those with normal uric acid levels.*

Conclusion: *High plasma uric acid level is a prognostic predictor in patients with CHF. Monitoring of uric acid may be useful for the management of patients with CHF.*

Key Words: *Heart failure; Prognosis; Uric acid.*

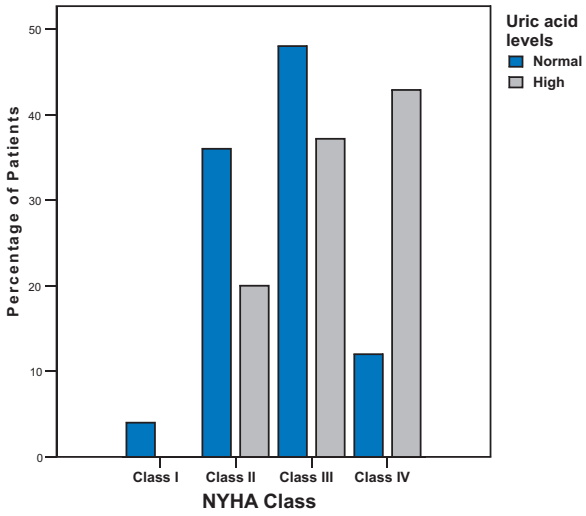
INTRODUCTION

Heart failure is defined as complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of ventricle to fill with or eject blood. Congestive heart failure (CHF) is the reason for at least 20 percent of all hospital admissions among persons older that 65 and over the past decade the rate of hospitalizations for heart failure has increased dramatically.[1] There is substantial evidence that oxidative stress participates in pathophysiology of cardiovascular disease. Biochemical molecular and pharmacological studies further implicate xanthine oxidoreductase (XOR) as a source of reactive oxygen species in cardiovascular system and may contribute to oxidative damage in the myocardium.[2] A chronic increase in myocardial oxidative stress is capable of causing subcellular abnormalities, and may lead to cardiomyopathic changes, depressed contractile function and failure.[3] Xanthine oxidoreductase (XO), which is physiologically present in the heart, catalyses the two terminal steps of purine metabolism, from hypoxanthine to xanthine and uric acid. Both steps also generate superoxide, and this ability to generate excess reactive oxygen species when the enzyme is unregulated, is central to the role of XO in heart failure.

Oxipurinol, the active metabolite of allopurinol and a potent xanthine oxidase inhibitor (XOI) is under evaluation as a novel agent for treatment of CHF. SUA seems to be a graded marker of predictor as well as for the development of cardiovascular mortality,[4] and increases in patients with chronic congestive heart failure (CHF) in numerous population studies.[5]

An elevated serum level of UA may relate to cardiac dysfunction and progression of heart failure through oxidative stress by increased XO activity in patients with CHF. However, there are no reports about whether UA is produced in the failing human heart or about the relationship between a transcardiac increase in serum UA and left ventricular dysfunction in patients with CHF. From a clinical perspective, these studies raise the

FIGURE 1 – BAR GRAPH SHOWING NYHA FUNCTIONAL CLASS DISTRIBUTION AMONG PATIENTS WITH NORMAL AND HIGH URIC ACID



issue of whether serum UA should be routinely measured in CHF patients. The present study was carried out to see:

1) The relationship of uric acid levels to functional class in CHF.
2) Duration of hospital stay and
3) 30-day mortality and rehospitalization rate.

MATERIAL AND METHODS

This descriptive cross sectional study was performed in Department of Medicine Fauji Foundation Hospital Rawalpindi. The objective of this study was to determine the prognosis in terms of indoor stay and mortality rate in CHF patients with normal or high uric acid levels. Hospital stay of more than 5 days was considered as worse outcome.

Inclusion Criteria

Data of patients of both genders with 20-80 years of age who were clinically diagnosed as chronic heart failure along with echocardiographic evidence of systolic/diastolic dysfunction and ejection fraction less than 50% was collected with convenience sampling, non-probability technique.

Exclusion Criteria

Patients already diagnosed hyperuricemia, patients already on uricosuric agents, patients already diagnosed as asthmatics, chronic obstructive pulmonary disease (COPD), respiratory tract infection and with renal failure were excluded from study.

The patient's venous blood samples were taken for serum uric acid level to be done in same laboratory and all patients had undergone 2D echocardiography. Data about variables: including age, gender, uric acid levels, duration of hospital stay, and outcome of patient was recorded on a specially designed performa.

Informed consent was taken from all patients as a part of ethical concern. Medical history along with physical examinations was performed for each participant at every clinic visit. Systolic and diastolic blood pressure was measured twice in the left arm of seated participants. The average of the two readings was used for each blood pressure variable. Height and weight were measured at each examination, and body mass index was calculated as the weight in kilograms divided by the square of the height in meters. Participants who reported smoking at least one cigarette per day during the year before the examination were classified as current smokers. Alcohol use was ascertained by self-report and was categorized as ounces of ethanol consumed per week. Menopause was defined as the absence of menses for 1 year or more. Serum uric acid levels were measured with an autoanalyzer that used a phosphotungstic acid reagent.[6]

All collected data regarding the patients is analyzed using SPSS version 10, data base software. Mean and standard deviation is calculated for age and hospital stay. Frequencies and percentages are presented for gender and outcome of the patient. Chi-square test is used as a test of significance, to compare the uric acid level with hospital stay, age, and gender and outcome of the patients. P-value of < 0.05 is considered significant. The Pearsons correlation coeffient is used to describe the linear relations.

RESULTS

The study included 66 patients of heart failure diagnosed on the basis of an ejection fraction < 50% out of which 6 patients lost follow up at some stage of data collection and were excluded. Baseline characteristics of patients in normal and high uric acid group are shown in Table 1. Mean age was 57.18 16.16 years with minimum of 18 and maximum age was 90 years. Forty one patients (68.3%) were males and rest of 19 (31.7%) were females. The mean age of male patients was 57.15 16.16 years and of females was 57.1517.79 years. The mean uric acid level was 7.71832.38 (range, 3.5 to 13.5 mg/dL). The mean uric acid level in men was 7.58782.29 (range 3.5 to 13 mg/dl) and in women was 8.0 2.59 (range, 3.9 to 13.5 mg/dL). The men and women did not differ significantly with respect to the mean serum uric acid levels (p= 0.537). Thirty five patients (58.33%) had high uric acid levels (25 (61%) male patients and 10 (52.6%) female patients had high

BASELINE CLINICAL CHARACTERISTICS FOR NORMAL AND HIGH URIC ACID GROUPS

Characteristic	Normal UA 25 (41.7%)	High UA 35 (58.3%)	P value
UA (mg/dL)	5.46 ± .882	9.311 ± 1.72	0.00
Age	51.6 ± 15.7	61.14 ± 15.48	0.023
Gender			
Males	16 (64%)	25 (71.4%)	0.542
Females	9 (36%)	10 (28.6%)	
NYHA functional class			
I	1 (4%)	0	
II	9 (36%)	7 (20%)	0.049
III	12 (48%)	13 (37.1%)	
IV	3 (12%)	15 (42.9%)	
CHF CLASS			
MILD HEART FAILURE (NYHA functional class I/II)	10 (40%)	7 (20%)	0.09
SEVERE HEART FAILURE (NYHA functional class III/IV)	15 (60%)	28 (80%)	
Etiology (IHD)	22 (88%)	31 (88.57%)	0.946
Risk factors			
-Diabetes mellitus	10 (40%)	14 (40%)	1.00
-Hypertension	2 (20%)	20 (57%)	0.004
-Hypercholesterolemia	7 (28%)	10 (28.6)	0.961
Duration of hospitalization	5.48 1.56	7.6 2.17	0.00
Hospitalization >5 days	8 (32%)	29 (82.9%)	0.00
Rehospitalization	3 (12%)	8 (22.9%)	0.284
30 day mortality	1 (4%)	3 (8.6%)	0.484

Compared using independent samples T- test
Compared using Chi square test

Table 1

uric acid levels). The Pearsons correlation coefficient for the relation of age and uric acid level was r = 0.150 (p= 0.253), hence, although the relation is positive but not significantly strong.

In the high UA group 0, 7 (20%), 13 (37%) and 15 (43%) were in NYHA functional class I, II, III and IV respectively. In the normal UA group 1 (4%), 9 (36%), 12 (48%) and 3 (12%) were in NYHA functional class I, II, III and IV respectively (as shown in figure 1). This difference among the two groups was statistically significant; p=0.049. Forty percent of patients were in mild to moderate heart failure (NYHA I and II) in normal UA group whereas only 20% had mild to moderate heart failure (NYHA I and II) in high UA group. Frequency of severe heart failure was 60% and 80% in normal versus high UA groups respectively. (p=0.09) Among the 24 diabetic patients 14 (58.3%) had hyperuricemia, whereas among the 36 non-diabetic patients 21 (58.3%) had hyperuricemia. This difference was not statistically significant; p= 1.00. Among the 25 hypertensive patients 20 (80%) had hyperuricemia and among the 35 normotensive patients 20 (57.1%) had hyperuricemia. This difference was again statistically significant; p=0.004. Among the 17 hypercholesterolemia patients 10 (58.8%) had hyperuricemia and among the 43 normotensive patients 25 (58.1%) had hyperuricemia. This difference was not statistically significant; p= 0.961.

Mean duration of hospital stay in the normal UA group was 5.4800 1.55 days as compared to patients in the high UA group and this difference was statistically significant, p= 0.00. Among the high UA group 29 (82.9%) patients stayed for 6 or more days while in the normal UA group only 8 (32%) patients stayed for

6 or more days and this difference was again statistically significant; p= 0.00. In the high UA group 3 patients died within 30 days of initial admission and their uric acid levels were 11.8, 13, 13.5 respectively and only one death occurred among the normal UA group, and this patient had a serum uric acid level of 6.2 mg/dl. The difference in the frequency of 30-day mortality among the high and normal UA groups was not statistically significant, p= 0.484.

Among the high UA group 8 (23%) patients required rehospitalization within 30 days of initial discharge. In six patients it was due to worsening dyspnea, in one it was due to new myocardial infarction and in one it was due to fever secondary to a urinary tract infection. Among the normal UA group only 3 (12%) required rehospitalization within 30 days of discharge.

The difference in the 30-day re-hospitalization frequency among the normal and high UA groups was not statistically significant, p= 0.284.

DISCUSSION

Average serum uric acid levels and hyperuricemia prevalence are higher in hypertensive subjects than in normotensive subjects. Whether or not hyperuricemia is an independent risk factor for cardiovascular diseases (CVDs) has been debated; however, it is widely recognized as a good indicator of the incidence of CVDs, especially in hypertensive subjects [7]. Several epidemiological studies have suggested that hyperuricemia may be an independent risk factor for CVDs. [8] Hyperuricemia *per se* has been reported to increase blood pressure [9] and to stimulate vascular smooth muscle proliferation and vascular remodeling. [10]Thus, the management of hyperuricemia in hypertensive subjects has been considered an important candidate to decrease the incidence. In Japan, guidelines for the management of hyperuricemia and gout were announced by the Japanese Society of Gout and Nucleic Acid Metabolism in 2002, and careful management of the serum uric acid level was proposed. [11] Although a recent report indicated that increased serum uric acid is an independent predictor of mortality in individuals with ischemic heart disease[12], the specific role of serum uric acid in relation to cardiovascular disease remains unclear. The association between serum uric acid and other cardiovascular risk factors complicates the issue. Increased serum uric acid levels are often accompanied by obesity, dyslipidemia, and hypertension, all of which are associated with increased risk for cardiovascular disease. Zimmet [13] proposed the concept of syndrome X and suggested a relationship between uric acid and the multiple risk factor-clustering syndrome. A recent study of Japanese men showed total cholesterol to be an independent correlate of serum uric acid levels after adjusting for BMI and triglyceride.[14] In the Coronary Artery Risk Developments in Young Adults (CARDIA) study, HDL cholesterol was lower among hyperuricemic subjects than nonhyperuricemic subjects both in men and women.[15] Several studies have reported that plasma uric acid levels were negatively associated with the occurrence of diabetes in men[3].

Mechanisms by which uric acid may be associated with atherosclerotic disease remain uncertain. A large body of evidence links uric acid with the metabolic syndrome of insulin resistance, obesity, hypertension, and dyslipidemia[14]. Several studies have shown an inverse relation between uric acid excretion and insulin level. Cappuccio and colleagues[16] reported an association of hyperuricemia with increased renal tubular sodium reabsorption, thus providing a link with hyperuricemia, hypertension, and hyperinsulinemia. Uric acid may also be an indicator for increased oxidative stress. Xanthine oxidase, a critical enzyme in the degradation of purines to uric acid, has been shown to be an important source of superoxide free radicals. The activity of xanthine oxidase increases during ischemia and intensifies during reperfusion in coronary endothelial cells[17]. In animals, allopurinol limits infarction size and enhances recovery of stunned myocardium,[18] perhaps by limiting the generation of toxic free radicals. A recent study suggested that xanthine oxidase is activated in congestive heart failure (CHF). However, whether uric acid (UA) is secreted from the failing heart remains unknown[19]. Despite having heart failure and being on loop diuretic therapy, most of the patients studied may have urate levels within normal limits.[20] Nevertheless, XO inhibition resulted in significant improvements to endothelial function as some studies have shown improved cardiac function and structure after long-term allopurinol treatment in CHF patients.[21] The primary effect of allopurinol could be the improvement in endothelial function that has resulted in better myocardial perfusion, thereby improving LV function. Alternatively, the improvement in endothelial function could be secondary to a direct effect of allopurinol on LV function through improvement in myocardial energetic efficiency and oxygen consumption.[22] Interestingly, even if improving LV function did contribute to improved endothelial function, the underlying mechanism could still be due to oxidative stress reduction as oxidative stress is a known mediator of adverse LV remodeling.[23]Anker et al in Germany reported that a high UA level

predicted mortality and indicated the need for transplantation in patients with CHF. [24] Altered renal excretion of UA caused by renal impairment or diuretics may contribute to hyperuricemia in CHF, so it is unclear whether serum UA is an independent prognostic predictor in relation to renal dysfunction in patients with CHF.

Data from local studies is also showing some supportive results regarding the relationship of high uric acid and cardiovascular morbidity and mortality. To find out the association of serum uric acid with type 2 diabetes mellitus and to compare the level of serum uric acid between obese and non-obese type 2 diabetics a local study showed the mean level of serum uric acid 6.07 mg/dl in obese type 2 diabetic patients as compared to 5.01 mg/dl in the control group. The difference was significant statistically and authors therefore concluded that hyperuricemia is significantly associated with type 2 diabetes mellitus and have increased morbidity and mortality from diabetes.[25] To find out possible relationship between serum uric acid and incidence of ischemic heart disease a comparative study was carried out at Basic Medical Science Institute, JPMC, Karachi. Serum uric acid was found to be significantly high ($P<0.001$) in hypertensive with ischemic heart disease and in hypertensive patients. The mean values were also found to be high in normotensives with IHD but the difference was statistically non-significant.[26] In another study the levels of serum uric acid and lipid profile was compared in patients with essential hypertension with levels of normal healthy individuals and results showed increased level of serum uric acid and lipid parameters in patients with essential hypertension except for HDL cholesterol which was significantly decreased as compared to the control subjects.[27]

Our study had certain limitations. More robust results could have been achieved by improving the sample size. Moreover, patients were followed for only 30 days and by increasing the duration of follow up to at least 6 months to one year would have provided a better assessment of differences in mortality between the two groups. Similarly, the two groups differed significantly with respect to their age distribution; patients in the high UA group were older than the normal UA group, and therefore the differences in the UA levels, higher mortality, prolonged duration of hospital stay and higher rehospitalization frequency could be because of older patients in this group. For this reason logistic regression analysis while controlling for age would have provided a more accurate assessment of the correlation of different variables.

In summary the recognition that uric acid plays a significant role in cardiac function should be appreciated. About 50 years ago it was recognized that gout and high uric acid levels were often a marker for coronary heart disease, Since then the literature has contained several hundred studies which have demonstrated a great deal of the physiology of xanthine oxidase inhibition. A reduction in xanthine oxidase improves cardiac output, improves endothelial function, reduces myocardial infarct size, reduces inflammation, and reduces myocardial oxidative stress and platelet adhesiveness. It seems logical that these effects would be beneficial to patients with congestive heart failure. In our study patients with high uric acid levels were mostly in severe heart failure, required significantly more rehospitalization, their duration of hospital stay was significantly longer and had more deaths within 30 days of follow up as compared to those with normal UA levels. Moreover, frequency of hypertension was significantly higher among the high UA patients.

CONCLUSION

Serum uric acid levels are a predictor of poor prognosis in patients with congestive heart failure. Further studies are warranted to evaluate its prognostic implications and potential utility in the monitoring of therapy and as a target of treatment for improving survival in heart failure. Adding uric acid levels to the assessment of cardiovascular risk might contribute to the improved ability to stratify risk in heart failure.

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