FREQUENCY OF HYPERURICEMIA IN PATIENTS WITH CORONARY ARTERY DISEASE AND ITS ASSOCIATION WITH DISEASE SEVERITY, AGE, GENDER, DIABETES MELLITUS, AND HYPERTENSION

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ABSTRACT

Objective: To determine frequency of elevated serum uric acid levels in patients with coronary artery disease, association of hyperuricemia with severity of coronary artery disease, gender, age, hypertension, and diabetes mellitus.

Study Design: Cross-sectional study.

Place and Duration of Study: Internal Medicine department, Combined Military Hospital Multan, from Nov 2015 to May 2016.

Methodology: One hundred and fifty patients with coronary artery disease were selected consecutively and admitted for coronary angiography. Serum uric acid levels were evaluated after eight hours fasting by photometric technique having normal reference range of 3.5-6.7 mg/dL. Coronary angiography was performed and Gensini score computed. To compare mean Gensini score between normouricemic and hyperuricemic population, student's t-test was applied.

Results: A total of 150 study cases (mean age: 54.4 ± 8.5 years), 101 (67.3%) were male while 49 (32.7%) were female. Diabetes mellitus was present in 43 (28.7%) of cases and hypertension was present in 65 (43.3%). Hyperuricemia was noted in 58 (38.7%) of cases. The mean Gensini score in hyperuricemic patients was significantly higher (40.31 ± 14.64) compared to patients with normal serum uric acid levels (25.02 ± 10.94) (p<0.001). The frequency of hyperuricemia was significantly higher in males, patients ≤60 years of age, and patients with diabetes mellitus (p<0.001, p=0.001 and p=0.001). No significant asso-ciation with hypertension was observed (p=0.314).

Conclusion: Frequency of 38.7% for hyperuricemia was noted in our study among patients with coronary artery disease. Hyperuricemia was significantly associated with higher Gensini score, male gender, younger age, and diabetes mellitus.

Keywords: Association, Coronary artery disease, Diabetes mellitus, Gensini score, Hyperuricemia, Hypertension.

INTRODUCTION

It has been observed that hyperuricemia is associated with cardiovascular risk factors for coronary artery disease (CAD) like male sex, old age, diabetes mellitus (DM), hypertension, insulin resistance, and hypertriglyceridemia[1]. It has also been proved in different studies that there is a strong association between serum uric acid (SUA) levels and adverse outcomes in CAD especially in patients with heart failure[2].

SUA is the end product of purine metabolism. It has been found that increased SUA is associated with endothelial dysfunction[3], anti-proliferative effects, high oxidative stress, generation of free radicals, and thrombus formation, all promoting atherosclerosis and its sequelae[4]. Endothelial dysfunction is regarded as the main mechanism by which hyperuricemia promotes atherosclerosis. Markers of endothelial dysfunction like albuminuria and plasma endothelin concentration are significantly increased in patients with persistent hyperuricemia.

Coronary angiography is the gold standard for diagnosis of CAD. The Gensini scoring system and the Syntax scoring system are the two most widely used scoring systems for assessing angiographic severity and complexity of CAD[5]. Studies have proved their correlation and comparability, with none of them inferior to the other[6]. Gensini scoring system, first introduced in 1975, gives weightage to the proximity of lesions within the coronary tree in addition to degree of stenosis; the lesions in the left main coronary artery getting the maximum score[7]. The final score is a true reflection of severity of CAD as it sums up cumulative effect of all lesions. It has also been shown to give more valuable prognostic information.

Although enough evidence is available that shows causal relationship of hyperuricemia and CAD, hyperuricemia, as an independent risk factor of CAD is yet to be established and treatment of asymptomatic hyperuricemia still needs to be introduced like statins

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Received: 31 Dec 2018; revised received: 27 Aug 2019; accepted: 27 Aug 2019

being used for the prevention of hypercholesterolemia in CAD. The rationale of this study was to determine the frequency of elevated SUA levels in patients with CAD and association of severity of CAD with hyperuricemia. Assessment of relationship of hyperuricemia with gender, age, hypertension, and DM were secondary goals.

METHODOLOGY

This cross-sectional study was conducted at the department of Internal Medicine of Combined Military Hospital, Multan, from November 2015 to May 2016. A sample size of 150 patients was calculated for this study using the WHO Sample size calculator for estimating a population proportion with specified absolute precision. Confidence interval of 95% and absolute precision of 8% was used with anticipated population size of 41%[1]. Through non-probability consecutive sampling, 164 newcases of CAD with age ranging from 45-75 years were included. Fourteen patients with heart failure, renal failure, myeloproliferative and lymphoproliferative disorders, chronic infections, and on alcohol and drugs causing hyperuricemiawere excluded.

The approval of ethics committee of Combined Military Hospital, Multan was sought prior to commencement of the study and informed consent was taken from the patients. All confounding variables were identified and excluded through exclusion criteria. The patients were admitted for coronary angiography either via outdoor patient department or emergency reception. SUA levels were evaluated after eight hours of fasting and analyzed with Mindray BS-400 chemical analyzer by photometric technique having normal reference range of 3.5-6.7mg/ dL. Coronary angiography was performed during the same hospital admission through right femoral route by Judkin's technique on Integrus H5000F (Philips) by two experienced cardiologists. Reporting of coronary angiogram was done by a consultant cardiologist unaware of clinical or biochemical profile of the patients. The Gensini score was used to evaluate the severity of atherosclerotic lesions on angiogram. The Gensini score was computed by assigning a severity score to each coronary artery stenosis according to the degree of luminal narrowing (visual assessment). This number was then multiplied by a factor that took into account the geographical importance of the lesion position in the coronary arterial tree. The Gensini score was then expressed as sum of scores of all coronary arteries.

Data analysis was performed using SPSS V 20.0. The sample was divided into two groups based on age (age ≤60 years and age >60 years). For quantitative variables like age and Gensini score, means and standard deviations were calculated. For qualitative variables like gender, hyperuricemia, and severity of CAD, frequencies and percentages were calculated. To compare mean Gensini score between normouricemic and hyperuricemic population, student's t-test was applied and *p*-value ≤0.05 was taken as significant.

RESULTS

This study comprised of 150 patients meeting inclusion criteria of our study. Of these 150 study cases, 101 (67.3%) were male patients while 49 (32.7%) were female patients. Mean age of our study cases was 54.4 ± 8.5 years (range: 45-74 years). Mean age of the male patients was noted to be 54.5 ± 7.6 years while that of female patients was 60.4 ± 8.8 years (p=0.001). This study results indicated that majority of our study cases i.e. 96 (64%) were aged ≤60 years.

Of these 150 studied cases, 60 (40%) belonged to rural areas and 90 (60%) belonged to urban areas. DM was present in 43 (28.7%) of our study cases and hypertension was present in 65 (43.3%) of our study cases.

Mean SUA level of our study cases was noted to be 6.58 ± 2.24 mg/dl and hyperuricemia was noted in 58 (38.7%) of our study cases. Mean Gensini score was 30.93 ± 14.52. The mean Gensini score in hyperuricemic patients was significantly higher (40.31 ± 14.64) as compared to patients with normal SUA levels (25.02 ± 10.94) (p<0.001).

The frequency of hyperuricemia was significantly higher in males, patients ≤60 years of age, and patients with DM (p<0.001, p=0.001, and p=0.001). No significant association with hypertension was observed (p=0.29) (table).

Table: Showing association with hyperuricemia.

Variables	Hyperuricemia		*p*-value
	Yes (n=58)	No (n=92)	
Gender			
Male (n=101)	53 (91.4%)	48 (52.2%)	<0.001
Female (n=49)	05 (8.6%)	44 (47.8%)	
Age			
<60 Years (n=96)	47 (81%)	49 (53.3%)	0.001
>60 Years (n=54)	11 (19%)	43 (46.7%)	
Diabetes Mellitus			
Yes (n=43)	38 (65.5%)	05 (5.4%)	<0.001
No (n=107)	20 (34.5%)	87 (94.6%)	
Hypertension			
Yes (n= 65)	22 (37.9%)	43 (46.7%)	0.29
No (n=85)	36 (62.1%)	49 (53.3%)	

DISCUSSION

CAD is one of the most common causes of mortality and morbidity in both developed and developing countries. It is one of the leading causes of death in Pakistan and its contribution to mortality in young patients is rising. Projections show that CAD has reached epidemic proportions in many developing countries. Heart diseases are rising in Asian countries and develop 5-10 years earlier than in other populations around the world. CAD that manifests at a younger age can have devastating consequences for an individual, the family, and society. Prevention of these deaths in younger people is a nation's moral responsibility. A strategy involving prevention of CADs long before their onset will be more cost-effective than providing interventions at a stage when the disease is well-established[6].

In accordance with previous studies, age was confirmed as a significant risk factor for hyperuricemia in our study and the odds of having higherserum UA levels were more in younger people than older people. Borghi and colleagues also observed stronger association of hyperuricemiawith younger subjects than older ones[8]. Another study has found similar trend in males but an opposite trend in females[9]. Other studies have observed a direct relationship of rising SUA levels with advancing age[10-13]. The increase in SUA level with age may be related to normal and efficient purine metabolism and reduced excretion of its by-product i.e. uric acid by the kidneys that declines with age.

The males in our study had a significantly higher frequency of hyperuricemia than females. The possible reasons for the greater prevalence of hyperuricemia in males is probably related to the dietary customs prevalent in our society. Males being considered the bread winners for the family are given greater share of high protein diet during childhood and working age. Males are also more inclined to the intake of soda drinks and alcohol, all of which increase SUA levels. Thus, males are expected to have higher chances of hyperuricemia than females. Similar results have been observed from Nepal[14], Nigeria[11], Ukraine[12], Japan[15], and China[16]. Nevertheless, some studies have reported higher prevalence in females also[8,17].

We did not find any significant association of hyperuricemia with hypertensionwhich is contradictory to many previous studies as hyperuricemia and hypertension are thought to contribute to each other[18]. Feig and Johnson found that about 90% of adolescent hypertension was associated with hyperuricaemia[19]. SUA is produced by the action of xanthine oxidase on purines and has been shown to cause hypertension and arteriolopathy through activation of the renin-angiotensin system and inhibition of nitric oxide (a potent vasodilator) production[20]. Xanthine oxidase activity also produces reactive oxygen species, namely superoxide, hydrogen peroxide, and the hydroxyl radical[20]. Reactive oxygen species cause tissue damage and in activate nitric oxide, leading to endothelial dysfunction, atherosclerosis, vasoconstriction, and vascular injury[20]. Drugs that inhibit xanthine oxidase activity, reduce production of SUA, improve bioavailability of nitric oxide, and thus result in lowering of blood pressure[20,21].

Several reports have suggested a relationship between SUA levelsand hyperglycemia in diabetic subjects[22-25]. Manyreports advocated a rise in SUA levels indiabetic subjects[22-25] as observed by us, while few disproved such statements. The causal relationship results as sub-normal insulin levels or insulin resistance seen in type 2 DM may decrease the activity of many glycolytic and citric acid cycle enzymesas insulin is a known promoter of these enzymes. Such a decrease in the activity of these enzymes leads to accumulation of glucose-6-phosphate, which may be channeled through Hexose Monophosphate Pathway causing an increase in ribose-5-phosphate which is the starting compound for purine biosynthesis. Thus, purine synthesis increases resulting in an elevated formation of SUA.

SUA levels predispose a person to development of CAD as revealed by significantly higher mean Gensini score in hyperuricemic patients as compared to normouricemic patients in ours study. Qureshi *et al*[1] also reported mean Gensini score in normouricemic group as significantly lower (22.15 ± 21.52) than hyperuricemic patients (35.69 ± 26.8) which is in compliance with our study results. It is also reported significantly higher levels of Gensini score in patients with hyperuricemia. It is observed that SUA levels were associated with the presence and severity of CAD inpatients who underwent coronary angiogra-phy. SUA is an independent determinant of severity of CAD in patients with mild-to-moderate chronic kidney disease.

The underlying mechanisms linking SUA and cardiovascular mortality have not yet been clearly demonstrated. SUA behaves as pro-oxidant at higher than normal levels and promotes formation of free radicals, platelet adhesiveness and aggregation as well as thrombusformation[3,4,20]. High levels of SUA are

associated with endothelial dysfunction, antiproliferative effects, impairednitric oxide production, lipid peroxidation, and smooth muscleproliferation[3,4,20]. It is suggested that hyperuricemia causes microvascular damage in the renal vascular bed and exacerbate vascular disease. Thus all these factors play a pivotal role in progression to CAD.

Association of hyperuricemia with severity of CAD may also be employed as prognostic tool in the patients with CAD, so, early diagnosis and proper management can help reduce adverse clinical outcomes. This will improve quality of life of these patients and will save them from future major adverse cardiac events and will also decrease burden on healthcare system.

CONCLUSION

A frequency of 38.7% for hyperuricemia was noted in our study among patients with CAD. Hyperuricemia was significantly associated with higher Gensini score, male gender, younger age, and DM.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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