Correlation between Serum Uric Acid level and Left Ventricular Ejection Fraction in Patients with Congestive Heart Failure

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ABSTRACT

Background: One of the risk factors of congestive heart failure that still under investigations is hyperuricemia. It's still debatable whether it's an independent risk factor or it's just a consequence of other disorders associated with cardiovascular diseases like hypertension, diabetes and dyslipidemia.

Objective: The aim of our study is to elucidate whether in patients with heart failure serum uric acid level correlated with left ventricular ejection fraction supporting the possibility that the detection of progressive hyperuricemia in these patients may be an indicator of deteriorating cardiac function.

Methods: We conducted a prospective study that included 124 studied patients and 26 apparently healthy persons at Coronary care unit and Internal Medicine Department at Sohag University Hospitals. All studied populations were classified into four groups;

- Group "I" patients being newly diagnosed heart failure,
- Group "II" patients decompensated heart failure on regular treatment,
- Group "III" patients decompensated heart failure but stopped their treatment from three months,
- Group "IV" control group selected to our study healthy and age-matched subjects from 30 to 70 years old .

Then we studied the association between left ventricular ejection fraction, the severity of congestive heart failure and the serum uric acid levels and the well-known conventional risk factor that include age, sex, BMI, positive family history, smoking, hypertension, diabetes and dyslipidemia then through logistic regression analysis we tried to identify the independent predictors of coronary artery diseases.

Results: The mean finding in our study is the significant higher mean ± SD serum uric acid levels in patients with congestive heart failure (8.43±2.95) versus apparently healthy persons (5.55±1.48) with "P value = .02". When we adjusted the serum uric acid with others significant factors in the univariate analysis which were age, gender and smoking, serum uric acid was an independent risk factor "P value = .04". Another interesting finding is significant correlation between serum uric acid level and the severity of congestive heart failure "P value<0.001,correlation coefficient=.35", where, that high rates of serum uric acid levels were recorded in patients with severe congestive heart failure. The gold finding is significant correlation between serum uric acid level and left ventricular ejection fraction "P value<0.001, correlation coefficient=.35", where, that high rates of serum uric acid levels were recorded in patients with reduced ejection fraction. According to ROC analysis a uric acid level of 8.45 mg/dl was found to be the most appropriate cut-off point with the sensitivitv 62% and the specificity 75%.

Conclusion: Higher serum uric acid levels are significantly correlated with the severity of congestive heart failure and left ventricular ejection fraction, as follows, the mean finding in our study is the significant higher mean ± SD serum uric acid levels in patients with congestive heart failure (8.43±2.95) versus apparently healthy persons (5.55±1.48) with "P value = .02". When we adjusted the serum uric acid with others significant factors in the univariate analysis which were age, gender and smoking, serum uric acid was an independent risk factor "P value = .04".

Keywords: Serum uric acid, congestive heart failure and left ventricular ejection fraction

INTRODUCTION

Uric acid (UA) is the end product of purine breakdown and is excreted by the kidneys. The enzymes responsible for the uric acid breakdown and production is xanthine oxidase and xanthine dehydrogenase. Both enzymes catalyze the oxidation of hypoxanthine to xanthine; this is a key enzyme in purine metabolism and the main contributor to the generation of oxygen free radicals which ultimately leads to increased oxidative stress.(1)Congestive heart failure is a leading etiology for both morbidity and mortality on a global level, resulting in an increase in both prevalence and health care costs. Recently, our understanding has changed from a mere hemodynamic condition to a much more complicated approach, including neuroendocrine and immune activation. Not only is the cardiovascular system damaged in the long run course of heart failure, but together with peripheral tissues and organs also result in the production of symptoms along with the progression of the disease.(2)

METHODS

We conducted a prospective study that included 124 studied patients and 26 apparently healthy persons at Coronary care unit and Internal Medicine Department at Sohag University Hospitals. All studied populations were classified into four groups; Group "I" patients being newly diagnosed heart failure,Group "II" patients decompensated heart failure on regular treatment,Group "III" patients decompensated heart failure but stopped their treatment from three months and Group "IV" control group selected to our study healthy and age-matched subjects from 30 to 70 years old

Exclusion criteria: The following groups of patients were excluded from the study on basis of clinical, electrocardiographic, echocardiographic and laboratory parameters:

Liver and kidney diseases, hematological or oncological disorders and patients taking diuretics, multivitamins, alcohol and on drugs interfering with serum uric acid levels. All cases in the study were examined for

1/Clinical history:

History of cardiovascular symptoms e.g. chest pain, shortness of breath, palpitation, syncope. History of previous myocardial infarction and history of any previous coronary revascularization procedure (PCI&CABG) and its details. Risk factors of coronary atherosclerosis particularly diabetes mellitus, hypertension, Hyperlipidemia, smoking, family history of coronary heart disease, gender, obesity, etc. Current medication and drug history (beta-blockers, calcium channel blockers, nitrates, aspirin, hypolipedemic drugs, etc.)

2/Full clinical examination with special stress on:

Body weight and height were measured pulse, blood pressure and respiratory rate. Examination of all peripheral pulses, particularly femoral arteries on both groins, and veins of lower limbs. Careful and complete cardiac and chest examination.

3/Investigations:

A/12 lead electrocardiography (ECG) :

Rate and Rhythm. ST segment changes as horizontal or down sloping ST depression 1 mm at the J-point in 2 contiguous leads or upward ST elevation represents myocardial injury. T-wave inversion at least 1 mm deep in 2 continuous leads that have dominant R waves (R/S ratio > 1). Pathological Q waves (indicate myocardial injury)

B/ Echocardiography (ECHO):

Study groups were examined at rest in supine left lateral decubitus position. Analysis according to the American Society of Echocardiography. Echocardiography is the most useful, widely available test in the diagnosis of heart failure with preserved ejection fraction (HFpEF) as an LVEF ≥50%, consider patients with an LVEF above 40% and less than 50% as heart failure with mid-range ejection fraction (HFmrEF) and consider patients with an LVEF ≤40% as heart failure with reduced ejection fraction (HFrEF).(3)

C/ Laboratory investigations:

Serum creatinine, liver function, Serum uric acid, lipid profile and serology, cardiac enzymes. The normal serum uric acid level ranges from 2.4–7.4 mg/dL in males whereas in females it ranges from 1.4–5.8 mg/dL. Hyperuricemia considered when serum uric acid level more than 7.4 mg/dl in males and more than 5.8 mg/dl in females. Serum uric acid level less than 8 mg/dl considered mild elevated, serum uric acid level between 8 mg/dl and 12 mg/dl considered moderate elevated and serum uric acid level more 12 mg/dl considered marked elevated. (4)

RESULTS

The mean age was 48.5 years ranging from 30 to 70 years. The mean BMI was 26.4. Most of studied populations were males representing 73.38% in studied patients and 61.54% in apparently healthy persons.The majority of studied patients were hyperuricemic with percentage of 79.83% and the opposite to this occurred to apparently healthy persons where 80.76% were non hyperuricemic. The mean uric acid level also recorded a marked difference as (8.87mg/dl) ranging from 4mg/dl to 14mg/dl in studied patients and 5 mg.dl ranging from 3.5mg/dl to 9mg/dl in apparently healthy persons. The mean of uric acid level of group who stop treatment, group regular on treatment, and group who newly diagnosed was 8.87, 8.35 and 7.1 respectively.The mean EF of group who stop treatment was 42%. The mean EF of group who regular on treatment was 43%, The mean EF of group who newly diagnosed was 44% and the mean EF of apparently healthy persons was 65%. Most of apparently healthy persons were preserved ejection fraction with percentage of 73.08%, while 69.23%, 63.33%, 60% of group who stop treatment, group regular on treatment, and group who newly diagnosed respectively were reduced ejection.For the severity of congestive heart failure, 30.77%, 40% and 27.27% of group who stop treatment, group regular on treatment, and group who newly diagnosed respectively were grade IV according to NYHA classification.

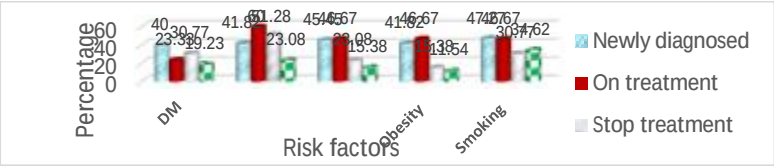
Comparison among the groups of studied populations as regard EF, NHYA classification.

Variable	Newly diagnosed N=55	On treatment N=30	Stop treatment N=39	Healthy N=26	P value
EF Mean ± SD Mean (range)	44.65±7.52 44 (28-58)	41.7±7.97 43 (25-55)	42.67±6.82 42 (22-55)	64.5±4.81 65 (57-72)	<0.0001
P1=0.40, P2=1.00, P3<0.0001, P4=1.00, P5<0.0001, P6<0.0001					
Degree of EF Preserved EF Mid-range EF Reduced EF	4 (7.27%) 18 (32.73%) 33 (60.00%)	0 (0.00%) 11 (36.67%) 19 (63.33%)	0 (0.00%) 12 (30.77%) 27 (69.23%)	19 (73.08%) 7 (26.92%) 0	<0.0001
P1=0.32, P2=0.21, P3<0.0001, P4=0.61, P5<0.0001, P6<0.0001					
NYHA No dyspnea Dyspnea with extra effort Dyspnea with normal effort Dyspnea with little effort	0 (0.00%) 0 (0.00%) 20 (36.36%) 20 (36.36%) 15 (27.27%	0 (0.00%) 0 (0.00%) 13 (43.33%) 5 (16.67%) 12 (40.00%)	0 (0.00%) 0 (0.00%) 11 (28.2%) 16 (41.03%) 12 (30.77%)	26 (100%) 0 0 0 0	<0.0001

Comparison among the groups of studied populations as regard degree of EF

Comparison among the groups of studied populations as regard NHYA

Comparison among the groups of studied populations as regard risk factors



DISSCUSSION

One of the risk factors of CHF that still under investigations is hyperuricemia. It's still debatable whether it's an independent risk factor or it's just a consequence of other disorders associated with cardiovascular diseases like hypertension, diabetes and dyslipidemia.(5)The possible effect of hyperuricemia on cardiovascular health may be related to its associated with endothelial dysfunction, anti-proliferative effects, high oxidative stress, generation of free radicals and thrombus formation, all promoting atherosclerosis and its consequences.(6) The controversy in the literature about the effect of hyperuricemia on cardiovascular health triggered us trying to study this association. Our study is a prospective study that included 124 studied patients and 26 apparently healthy persons who underwent echocardiography at Coronary care unit and Internal Medicine department at Sohag university hospitals. after exclusion of those patients with chronic liver, kidney diseases, hematological or oncological disorders, also patients who maintained on drugs that affect serum uric acid levels were excluded. All studied populations were evaluated using detailed history and examination, ECG , Echocardiography and labortary analysis of serum creatinine, lipid profile and serum uric acid. All studied populations were classified into four groups being newly diagnosed, on regular treatment or who stop treatment admitted to Coronary care unit and Internal Medicine Department of Sohag University Hospitals will be selected to our study and number of healthy age-matched subjects served as controls, then we studied the association between left ventricular ejection fraction, the severity of congestive heart failure and the serum uric acid levels and the well-known conventional risk factor that include age, sex, BMI, positive family history, smoking, hypertension , diabetes and dyslipidemia then through logistic regression analysis we tried to identify the independent predictors of coronary artery diseases. The mean age was 48.5 years ranging from 30 to 70 years. The mean BMI was 26.4. Apparently healthy persons from the same age selected to our study. The males ranked the largest proportion to the participants in the study with percentage of 73.38% in studied patients and 61.54% of apparently healthy persons were males.The majority of studied patients were hyperuricemic with percentage of 79.83% and the opposite to this occurred to apparently healthy persons where 80.76% were non hyperuricemic. The mean of uric acid level of group who stop treatment, group regular on treatment, and group who newly diagnosed was 8.87mg/dl, 8.35mg/dl and 7.1mg/dl respectively. While the mean of uric acid level of apparently healthy persons was 5mg/dl. These results coincided with a study was conducted **the Faculty of Medicine, Cairo University, 2015 entitled "Hyperuricemia in egyptian health system"**. This study included 778 studied patients and 148 of healthy age-matched subjects served as controls.Where, the mean age was 49 years ranging from 38 to 75years. The mean BMI was 25,6. Most of studied populations were males with percentage of 68%. The majority of studied patients were hyperuricemic with percentage of 63.5% and the opposite to this occurred to apparently healthy persons where 92% were non hyperuricemic. The mean of uric acid level of studied patients was 7.9mg/dl,while the mean of uric acid level of apparently healthy persons was

4.4mg/dl.(7) In the univariate analysis factors including age, gender, smoking habits and serum uric acid levels showed significant differences between both groups, other known risk factors for CHF were not significant, but this may be related to the small sample size and we think with increasing patients number other factors may turn significant.We observed higher association between hyperuricemia and hypertension, diabetes, dyslipidemia with higher BMI versus normouricemic patients and these results are in agree with the study "**Hyperuricemia and coronary heart disease" Seo Young Kim,2006"** and this explained by pathogenic role of uric acid in hypertension, also insulin resistance that present in association with metabolic syndrome has acausative role in developing hyperuricemia.(8) For the severity of congestive heart failure, 30.77%, 40% and 27.27% of group who stop treatment, group regular on treatment, and group who newly diagnosed respectively were grade IV according to NYHA classification. Hyperuricemic studied populations with serum uric acid level >12mg/dl, the majority of them 88.37% of them were heart failure grade IV and 11.63% were heart failure grade III. Hyperuricemic studied populations with serum uric acid level between 8to12mg/dl, 50.88% of them were heart failure grade III and 43.86% were heart failure grade II. Hyperuricemic studied populations with serum uric acid level between 6to8mg/dl, 38.10% of them were heart failure grade II, 19.05% were heart failure grade I, and 14.29% were heart failure grade III. Hyperuricemic studied populations with serum uric acid level<6 mg/dl, the majority of them (58.62%) had no dyspnea whereas 3.45% were heart failure grade IV. Our results revealed that high rates of serum uric acid levels were recorded in patients with severe congestive heart failure. Our results cope well with many previous studies that had a similar study design, Deveci et al conducted study on 1012 patients and he found significantly higher mean ±SD serum uric acid in coronary artery diseases (6.3 ± vs 5.4 ± 1.4, P value < .001) and high uric acid levels was an independent predictor in the multivariate analysis, in the linear regression analysis hyperuricemia showed a significant correlation with severity of congestive heart failure irrespective to gender.(9) According to ROC analysis a uric acid level of 6.45 mg/dl was found to be the most appropriate cut-off point with the sensitivity 57% and the specificity 78.5% which is close to results of Deveci et al; they found a uric acid level of 6.8 mg/dl to be the most accurate cut-off with 40 % sensitivity and 87.5 % specificity.(10) Also, our results converged with a study conducted at **the Faculty of Medicine, Mansoura University, 2017 entitled "Serum uric acid and atherosclerotic coronary artery diseases"**. This study included 95 patients classified into two groups ,49 patients with CAD and 46 patients with non CAD. This study found that significant higher mean ± SD serum uric acid levels in patients with CAD versus free patients (7.43±2.95 vs 5.55±1.48, P value = .02). Another interesting finding is significant correlation between serum uric acid level and the severity of CAD (P value<0.001, r=.35).(11) By echocardiography the mean of ejection fraction between studied patients was 43% ranging from 22% to 58%, where, the mean EF of group who regular on treatment was 43%, the mean EF of group who newly diagnosed was 44% and the mean EF of group who stop treatment was 42%. compared to the mean EF of apparently healthy persons

was 65% ranging from 57% to 72%. Most of apparently healthy persons were preserved ejection fraction with percentage of 73.08%, while 69.23%, 63.33%, 60% of group who stop treatment, group regular on treatment, and group who newly diagnosed respectively were reduced ejection. Correlation coefficient between serum uric acid level and EF-0.75 with P value <0.0001. Our results revealed that high rates of serum uric acid levels were recorded in patients with reduced ejection fraction. 95.35% of patients with reduced EF were hyperuricemic with serum uric acid level >12mg/dl, 56.14% of patients with reduced EF were hyperuricemic with serum uric acid level between 8to12mg/dl, 14.29% of patients with reduced EF were hyperuricemic with serum uric acid level between 6to8mg/dl, and13.79% of patients with reduced EF were non hyperuricemic with serum uric acid level<6. The majority of patients with mid-range EF (57.14%)were hyperuricemic with serum uric acid level between 6to8mg/dl**,** 41.38% of patients with mid-range EF were non hyperuricemic with serum uric acid level <6mg/dl, 38.60% of patients with mid-range EF were hyperuricemic with serum uric acid level between 8to12mg/dl, and 4.65% of patients with mid-range EF were hyperuricemic with serum uric acid level>12mg/dl.In the contrast 44.83% of studied populations with preserved EF were non hyperuricemic with serum uric acid level<6mg/dl, 28.57% of studied populations with preserved EF were hyperuricemic with serum uric acid level between 6to8mg/dl, and just 5.26% of studied populations with preserved EF were hyperuricemic with serum uric acid level between 8to12mg/dl. Our results cope well with an important study was carried at university of Palermo, Italy that included 1118 patients classified to three groups patients with systolic and diastolic dysfunction (EF<50% and E wave < A wave; n=40) , those with isolated diastolic dysfunction(EF>50% and E wave < A wave; n=24) and those that had a normal left ventricular function (EF>50% and E wave > A wave, n=54). All patients underwent echocardiography and laboratory test patients with diastolic dysfunction with or without systolic dysfunction showed higher values of serum uric acid than patients with normal ventricular function (6.54± 0.72 vs. 5.42 0.78, p=0.0116. The linear regression in in the group of patients with systolic dysfunction, showed an inverse relationship between the two variables analyzed, so with increasing serum uric acid there is aproportional reduction of EF.(12) Patients with isolated left ventricular diastolic dysfunction and patients with systolic and diastolic dysfunction had higher uric acid levels than patients with normal ventricular function and progressive of systolic function correlates with agradual increase in the values of serum uric acid. This study agreed with our results.

CONCLUSION

Higher serum uric acid levels are significantly correlated with the severity of congestive heart failure and left ventricular ejection fraction, as follows, the mean finding in our study is the significant higher mean ± SD serum uric acid levels in patients with congestive heart failure (8.43±2.95) versus apparently healthy persons (5.55±1.48) with "P value = .02". When we adjusted the serum uric acid with others significant factors in the univariate analysis which were age, gender and smoking, serum uric acid was an independent risk factor "P value = .04". Another interesting finding is significant correlation between serum uric acid level and the severity of congestive heart failure "P

value<0.001, correlation coefficient=.35", where, that high rates of serum uric acid levels were recorded in patients with severe congestive heart failure. But the gold finding is significant correlation between serum uric acid level and left ventricular ejection fraction "P value<0.001, correlation coefficient=.35", where, that high rates of serum uric acid levels were recorded in patients with reduced ejection fraction. According to ROC analysis a uric acid level of 8.45 mg/dl was found to be the most appropriate cut-off point with the sensitivity 62% and the specificity 75%.

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