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RELATION OF HYPERURICEMIA WITH HEART FAILURE IN MOSUL CITY

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ABSTRACT

Background: The relationship between levels of uric acid (UA) and cardiovascular disorders has been well-documented, and hyperuricemia is an old but reemerging metabolic illness. Numerous diseases, such as hypertension, myocardial infarction, metabolic syndromes, and heart failure (HF), are connected to rising uric acid levels. **Aim of the study:** To determine the extent of changes in the level of serum Uric Acid in each type of Heart failure (left-sided, right-sided and biventricular). **Patients, Materials and Methods:** A case-control study included 30 persons who appeared to be in good health as controls and 118 patients with heart failure as cases. The study was carried out between November 1, 2005, and May 15, 2006, in the medical ward, emergency room, and cardiac care unit (CCU) at Ibn-Sina general teaching hospital and Al-Salam general hospital. The full study sample's uric acid levels were examined. **Results:** Among the 118 cases with HF; 66 were males and 52 were females, the sample's mean age was 59.06 ± 10.13. BMI was 25.18 ± 3.04, current smoking found in 44.1% of them. While among the 30 controls; 16 were males and 14 were females, with mean age was 57.53 ± 5.19, the mean BMI was 25.70 ± 1.82, with 36.7% of the controls were smokers. Statistically significant differences were detected ($p<0.001$) in serum UA between each type of HF and the controls, but no significant difference found among the three groups of HF. According to the duration of HF, there was significantly higher level of UA in group C than group A ($p \leq 0.05$). While the difference of the UA levels among the different cut-off points for BMI was statistically not significant. The sensitivity of UA was 70.34 % and the specificity was 96.67 %. **Conclusions:** The current study concluded that Biventricular, left-sided and right-sided Heart failure led to hyperuricemia. Although different mechanisms may contributed to hyperuricemia, but the single exact mechanism that can explain the pathogenesis of hyperuricemia in Heart failure patients is still unclear. There is a direct relation between the duration of Heart failure and the elevation in serum Uric Acid concentration and no significant difference in hyperuricemia between the three categories of Heart failure (biventricular, left-sided and right-sided) was noticed.

KEYWORDS: Heart Failure, Hyperuricemia.

INTRODUCTION

The relationship between cardiovascular illnesses and uric acid (UA), an old yet reemerging metabolic condition, has been well documented. Increased uric acid levels are associated with a number of diseases, including hypertension, myocardial infarction, metabolic syndromes, and heart failure (HF).[1]

The last byproduct of undesired purine nucleotides' breakdown in humans is UA. In the human body, uracil scavenges potentially damaging radicals. The balance between urate generation and excretion, which controls serum urate levels, can however cause gout, nephrolethiasis, HT, and vascular disorders when combined with hereditary or environmental (particularly dietary) variables.[2]

Humans excrete about 75% of their UA in their urine, with the majority of the remaining 25% being released into the GI tract where it is broken down by bacterial enzymes into allantoin and other components. Renal handling of UA is complex process and involves four sequential steps:

1) Glomerular filtration.
2) Reabsorption of about 98% to 100% in the proximal convoluted tubule.
3) Secretion into the lumen of distal portion of the proximal tubule.

4) Further reabsorption in the distal tubule.

Net urinary excretion of UA is 6% to 12% of the amount filtered.[3]

Most frequently, plasma or serum UA concentrations greater than 420 mol/l in men or greater than 360 mol/l in women are used to identify hyperuricemia.[3]

Factors affecting plasma urate[4]:
1) Sex: plasma urate reference range is higher in males than females.
2) Obesity: UA tends to be high in obese.
3) Social class: the more affluent social class tends to have a higher plasma urate.
4) Diet: plasma urate rises in individual used to take a high protein diet. i.e. a diet that is also rich in nucleic acid and in those with a high alcohol consumption.
5) Genetic factors: are important.

Previous research has demonstrated that hyperuricemia and heart failure frequently go hand in hand.[5, 6] According to a small case study, patients with primary pulmonary hypertension, cor pulmonale, and dilated cardiomyopathy have higher left atrial pressure and lower cardiac index when they have hyperuricemia.[7] Hyperuricemia is a potential hazard factor for negative outcomes, including mortality, in people with well-known heart failure.[8–16]

For people who already have heart failure, serum uric acid may be helpful in predicting outcomes.[11–16] In people with pre-existing hypertension, hyperuricemia can predict heart failure.[17] Studies examining hyperuricemia as a stand-alone risk factor for occurrence of heart failure in the general population have not been conducted. The one study from Austria that is currently accessible did not control for potential confounders including renal disease, valvular heart disease, or diuretics, and it suggested that the highest quantiles of serum uric acid were linked to a raised risk of dying from heart failure.[18]

Aim of the study: To determine the extent of changes in the level of serum Uric Acid in each type of Heart failure (left-sided, right-sided and biventricular).

PATIENTS, MATERIALS AND METHODS

Patients

A case- control study design was adopted to achieve the aim of the study. The sample consisted of:

1. Patients: One hundred-eighteen patients with HF, age ranged (20-75) years with mean± standard deviation (SD) of 59.06±10.13 years and involved 52 females and 66 males.

All patients were diagnosed by physician as HF and on treatment, the diagnosis were done depending on:

- History and physical examination.
- CXR.
- ECG abnormalities.
- Echocardiography.

On admission, all of them had HF according to the Framingham criteria for the diagnosis of HF. The physician in the hospital has decided in which type of failure they were (left-sided, right-sided or biventricular), and what investigations and treatment they needed.

As a criteria for this study, all patients should have HF of cardiac causes without any other disease or condition that could affect the level of serum urate and neither clinical diagnosis nor ECG abnormalities should suggest ischemic cause for the deterioration in their cardiac function condition, except for the treatment of HF they were on, no other medications should interrupt with the study results by affecting the level of the tests.

2. Control group: which involved 30 healthy persons, of them 16 were males and 14 were females and they matched with the same age group of the cases were selected from the medical staff, relatives and attendants of the out patients clinic department, with neither HF, HT, renal or liver problems or DM (presumably or apparently healthy persons), nor medications affecting the result.

The study was conducted during the period from the 1st of November 2005 to the 15th of May 2006, in Ibn–Sina general teaching hospital and Al-Salam general hospital the cases were from the medical ward, emergency unit and cardiac care unit (CCU).

Both cases and control group were interviewed and the general information was taken to fill the questionnaire in the appendix.

Duration of the Disease

According to the duration of HF, patients were classified into three categories:

1. Group A (1-5 years).
2. Group B (6-10 years).
3. Group C (>10 years).

Types of Heart Failure

According to the definition and classification of HF, all of the patients had chronic decompensated HF, this decompensation had forced them to come to the hospital and was the cause for their admission, the types of HF were Left - sided HF, right - sided HF, and biventricular HF.

Materials

In this study, materials were arranged into specimens, instruments, and reagents.

Specimens

Blood samples were collected from all subjects by an antecubital venepuncture, and stressful Venipuncture was avoided.

Five milliliter (ml) of venous blood have been collected from every subject then allowed to clot in plane tube, the serum was separated by centrifuge at 3000 rpm for 5 minutes, and the resultant serum was used for biochemical testing of serum Urate concentration.

The samples were kept until analyzed at a weekly batches at (-20)° C.

Instruments: the instruments that were used in this study include centrifuge 3E-1 (sigma, Germany), Cecil, Ce 303, Greating spectrophotometer (Cambridge, England), and water bath Gallen Kamb (England).

Reagents

All laboratory reagents used through this study which were of analar grade, obtained from the clinical chemistry laboratory of the department of biochemistry, Mosul College of Medicine, they were purchased from international suppliers and companies and all reagents will be mentioned within the related methodologies.

Methods

Determination of Uric Acid Level in the Serum.

Serum urate was determined by uricase method[19] by using a kit method supplied by Biomerieux Company (France).

Principle

UA present in the sample determined according to the following reactions:

$$\text{Uric acid} + 2\,H_2O + O_2 \xrightarrow[\text{uricase}]{} \text{allantion} + CO_2 + H_2O_2$$

$$H_2O_2 + \text{3.5 dichloro-2-hydroxybenzene-sulfonic acid} + \text{4-aminoantipyrine} \xrightarrow[\text{Peroxide}]{} \text{Chromogen} + HCL + 2\,H_2O$$

Chromogens were measured by spectrophotometer at 520 nm

Reagents

Reagent 1 Standard	Uric acid	476 µmol/l (80 mg/l)
Reagent 2 Chromogen buffer	Tis buffer pH 8.0 3.5dichloro-2-hydroxybenzene sulfonic acid surface – active agent	50 mmol/l 2 mmol/l 2 mmol/l
Reagent 3 Enzymes	Uricase Peroxidase Ascorbate oxidase 4-aminoantipyrine	≥ 100 U/l ≥ 200 U/l ≥ 1000 U/l 0.25 mmol/l

Procedure

	Reagent blank	**Standard**	**Sample**
Reagent 1 (standard)	———	20 µl	———
sample	———	———	20 µl
Working solution	1 ml	1 ml	1 ml
Mix. Incubate for 5 minutes at 37°C or 10 minutes at between 20 and 25°C.			

Zero adjustment is by reagent blank; Measure at wavelength 520 nm (510-530), the color intensity is stable for 30 minutes.

Calculation

$$\frac{\text{Absorbency of sample}}{\text{Absorbency of standard}} \times n$$

n = concentration of standard

µmol/l : n = 476
mg/l : n = 80

Statistical analysis

The data collected during the study were summarized in sheets of Microsoft Excel 2007. The statistical analysis performed by using IBM-SPSS 26. The normality of these data tested by Shapiro-Wilk test, and the parametric tests were decided to be chosen. Nominal data was expressed in frequencies and proportions while numerical data was expressed in means and standard deviations. The Pearson chi square test (x^2) used for the nominal data. The numerical data were comparing by the t-test performed for independent two means between the controls groups and parameters studied groups. One-Way ANOVA and Duncan Multiple Range Test. P-value ≤ 0.05 considered as significant.

RESULTS

The demographic characteristics of the studied groups were showed in table (1). This table elicited that the cases were one hundred eighteen patients with HF (52 females and 66 males), age ranged from (20-75) years with a mean ± SD of (59.06 ± 10.13). While the control group were 30 apparently or presumably healthy persons of 16 males and 14 females, the age ranged from (28-66) years with a mean ± SD of (57.53 ± 5.19).

Table (1): Demographic characteristics of the studied groups.

Characteristics		Mean ± SD			
		Controls		Cases	
Age (year)		57.53 ± 5.19		59.06 ± 10.13	
BMI (kg/m^2)		25.70 ± 1.82		25.18 ± 3.04	
		No.	%	No.	%
Gender	Male	16	53.3	66	55.9
	Female	14	46.7	52	44.1
	Male: female	1.14		1.27	
Smoking	Smoker	11	36.7	52	44.1
	Non-smoker	19	63.3	66	55.9

Distribution of patients according to type and duration was displayed in table (2) and showed that there is significant difference (p-value <0.01) in the distribution of patients according to the type and duration of heart failure.

Table (2): Distribution of patients according to type and duration.

Duration (yr)	Type of HF						p-value*
	Biventricular HF		Left-sided HF		Right-sided HF		
	No.	%	No.	%	No.	%	
1-5	45	81.8	33	71.7	7	41.2	<0.01
5-10	10	18.2	8	14.7	7	41.2	
>10	0	0.0	5	10.9	3	17.6	
Total	55	100	46	100	17	100	

*Pearson Chi square test has been used

Comparison of measured parameters in control group and among HF patients according to type was showed in table (3) and demonstrated highly significant differences were detected (p<0.001) in serum UA between each type of HF and the controls. The post hoc test showed that there was no statistically significant difference for the UA level among the three groups of HF.

Table (3): Comparison of measured parameters in control group and among HF patients according to type.

Parameters	Mean ± SD			
	Controls * (n=30)	Cases (n=118)		
		Biventricular HF (n=55)	Left-sided HF (n=46)	Right-sided HF (n=17)
UA(µmol/l)	304.32 ± 73.6	446.78 ± 66.6 [a]	434.24 ± 78.5 [a]	431.88 ± 38.9 [a]

Means with different letters horizontally have significant difference at p≤0.05
* Significant difference from control group at p<0.001

Comparison of measured parameters in patients according to duration of heart failure was demonstrated in table (4). It elicited that according to the duration of HF, patients were classified into three categories: Group A (1-5), Group B (6-10), Group C (> 10) UA is significantly higher in group C than group A (p ≤ 0.05).

Table (4) Comparison of measured parameters in patients according to duration of heart failure.

Parameters	Mean ± SD		
	Duration (year)		
	Group A (n=85)	Group B (n=25)	Group C (n=8)
UA (µmol/l)	425.82 ± 65.18 [a]	474.56 ± 60.81 [bc]	478.88 ± 76.77 [c]

*One-Way ANOVA test has been used
Means with different letters horizontally have significant difference at p≤0.05

Comparison of measured parameters in patients according to BMI was showed in table (5) and revealed that the difference of the UA levels among the different cu-off points for BMI was statistically not significant.

Table (5): Comparison of measured parameters in patients according to BMI.

Parameters	BMI			p-value *
	Mean ± SD			
	<25	25-30	>30	
UA (µmol/l)	438.19 ± 66.5	444.91 ± 73.0	425.60 ± 60.1	NS

*One-Way ANOVA test has been used; NS = no significance

Distribution of the studied groups according to uric acid levels was demonstrated in table (6). This elicited that the upper reference range as a cut-off point, 70.3 % of the cases were higher than the cut-off level and 3.3 % of the control were higher than the cut-off level with significant difference (p <0.001). The sensitivity is 70.34 % and the specificity is 96.67 %.

Table (6): Distribution of the studied groups according to uric acid levels.

UA (□mol/l)	>420 (M) &>360 (F)		≤420 (M) &≤360 (F)		Sensitivity %	Specificity %	p-value
	No.	%	No.	%			
Cases	83	70.3	35	29.7	70.34	96.67	<0.001
Controls	1	3.3	29	96.7			

M=Male, F=Female.

DISCUSSION

All serious kinds of heart disease have a "final common pathway" that is represented by HF.[20] HF is a serious health issue that is becoming more common in the general population[21]; it is mostly the end stage of hypertensive, coronary, and VHD due to an aging population of a larger size and the extension of the lives of cardiac patients by contemporary medication.[22]

UA is a significant hazard factor for cardiovascular disease; numerous studies have demonstrated that, in addition to its link to the metabolic syndrome, it also acts as an independent risk factor for all cardiovascular events, including HT, atherosclerosis, ischemia, and stroke.[23-28]

Despite the fact that certain other researches[29, 30] were unable to show a substantial link between UA and cardiovascular illnesses.UA is a metabolic byproduct of purine metabolism.[16] It is produced in the final step of purine metabolism, which is catalyzed by xanthine oxidase, and it is lost primarily through renal excretion[31], with the kidney accounting for about two thirds and the digestive tract for the remaining third.

A direct pathophysiological involvement for the metabolic pathway that produces UA in the failing circulation and HF is being firmly supported by mounting data.[33]

UA is possibly protective since it can serve as an antioxidant both on its own and through enhancing superoxide dismutase activity. According to experimental research, UA itself may contribute to renal and cardiovascular pathology.[34] Allopurinol can counteract these hemodynamic and structural alterations. UA potently stimulates vascular smooth muscle cell proliferation in vitro, an action mediated by activation of mitogen-activated protein kinase, cyclooxygenase-2, and platelet derived growth factor.[35]

The purine bases adenine and guanine are broken down to create UA (32). Xanthine dehydrogenase or xanthine oxidase are the enzymes that catalyze the conversion of hypoxanthine into xanthine and this metabolite into UA in purine metabolism.[37] The latter enzyme originates from xanthine dehydrogenase in conditions of low oxygen tension (hypoxia), in the presence of certain pro-inflammatory cytokines[38] and possibly in response to some hormones, in addition to xanthine or UA, the chemical reactions catalyzed by xanthine oxidase produce superoxide anion free radicals. Superoxide interacts with protons and separately with nitric oxide to produce reactive oxygen species, which can harm

cardiovascular structures.[40] Superoxide also increases oxidative load by reducing antioxidant defenses like nitric oxide.[41]

In the endothelium of a man, xanthine oxidase is highly expressed, but it doesn't seem to be present in the myocardium.[42] In the present study, hyperuricemia was frequent among patients with HF (biventricular, left-sided and right-sided), serum UA is significantly higher in cases than that of control group with significant difference, but there is no significant difference in serum UA among the three types of HF and these results were in agreement with other studies which proved that HF is associated with hyperuricemia.[6, 7, 9, 43-45]

The sensitivity of serum UA test was (70.34%) and the specificity was (96.67%) with ($p<0.001$), by multiple logistic regression model for predictors of HF, the odd ratio for UA was high (8.11) with ($p<0.05$).

Although numerous additional investigations have indicated that biventricular, left-sided, and right-sided HF patients frequently have hyperuricemia, the underlying mechanisms that causing this high serum urate content are still unknown.[7]

There are a number of potential causes for the over production of UA in HF, including tissue hypoxia, which is known to increase ATP degradation and to stimulate the expression of xanthine oxidase[7], increased abundance and activity of xanthine oxidase[31], or increased conversion of xanthine dehydrogenase to xanthine oxidase[46] Hyperuricemia can also result from reduced excretion of UA, as xanthine oxidase catalyzes UA production in the two terminal steps, which also produces a molecule of super oxide for each reaction[46], the elevation in serum UA level may reflect an increase in xanthine oxidase pathway activity and, consequently, the generation of superoxide and resulting oxidative stress via the xanthine oxidase system.[47]

Contrarily, although it is likely that low cardiac output and venous congestion lead to impaired glomerular filtration and tubular excretion of UA, hormonal factors or circulating substances like catecholamines, angiotensin I, endothelin, thromboxane, ANP, or BNP may also be involved in the impaired removal of UA.[48]

Although the majority of HF patients were taking diuretics, other researchers had examined the effects of HF on serum urate concentration in patients with right-sided HF without diuretics and had found that hyperuricemia in HF cannot be explained solely by diuretic therapy.[7] These mechanisms may explain the reasons for hyperuricemia in the three types of HF (biventricular, left-sided, and right-sided), additionally, several investigations had demonstrated that the right atrial pressure was mostly linked with serum urate rise in right-sided HF patients who were not taking diuretics.[49]

The results of this study show that basal metabolic index did not affect serum UA concentration, but the duration of HF affects it's concentration and this is consistent with (Leyva et al, 1997).[6] Other studies (Leyva et al, 1997) have found that hyperuricemia of HF is independent of diuretic use, serum creatinine, fasting insulin, alcohol intake, basal metabolic index, and insulin sensitivity.[6] The finding that hypoxia in HF results in the accumulation of the precursors of UA (hypoxanthine and xanthine) and activation of the enzyme xanthine oxidase[6] suggests that over production is likely to be an important contributor, even though elevations in serum UA levels that are associated with hypoxic states have been attributed to diminished renal excretion.

CONCLUSIONS

The current study concluded that Biventricular, left-sided and right-sided Heart failure led to hyperuricemia. Although different mechanisms may contributed to hyperuricemia, but the single exact mechanism that can explain the pathogenesis of hyperuricemia in Heart failure patients is still unclear. There is a direct relation between the duration of Heart failure and the elevation in serum Uric Acid concentration and no significant difference in hyperuricemia between the three categories of Heart failure (biventricular, left-sided and right-sided) was noticed.

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