Possibility of association of hypertension and ischemic heart disease with primary hyperuricemia

Noor El-Deen Abd El-Azeem M. Elhefny[a], Mona H. Elzohri[b], Sara Mostafa Taher[c]

[a]Professor of Internal Medicine, Faculty of Medicine, Assiut University, [b]Associate Professor of Internal Medicine Department, Rheumatology and Clinical Immunology Unit Faculty of Medicine, Assiut University, [c]Resident Doctor of Internal Medicine Department, Assuit, Egypt

Correspondence to Sara Mostafa Taher, MSc, Department of Internal Medicine, Assuit University, Assuit, Egypt.
Zip Code: 256285;
Tel: +20 1062006694;
e-mail: sarabsbosa13@yahoo.com

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Background
The relations between serum uric acid and cardiovascular disease are complex, so in the past five decades, more than 40 epidemiologic and clinical studies involving up to 150 000 individuals have been carried out to assess this association.

Objective
This study aimed to investigate the association between high uric acid levels and cardiovascular disease and hypertension.

Patients and methods
A total of 40 patients with primary hyperuricemia selected from Internal Medicine Department, Rheumatology Unit, Assiut University Hospital, were included in this study. Age of the studied patients ranged between 23 and 87 years. None of the patients were diabetic, hypertensive, had ischemic heart disease, or were smoker. Moreover, none of them had gout, kidney diseases, or liver cirrhosis. All of the studied patients had normal abdominal ultrasonographic findings with normal urine analysis and normal BMI. Incident hypertension was defined as newly detected blood pressure of at least 140/90 mmHg, which was examined along with ischemic changes by echocardiography.

Results
Overall, 37.5% patients were discovered to be hypertensive and 32.5% patients had ischemic changes on echocardiography.

Conclusion
There is a strong and significant association between high uric acid levels and ischemic heart disease and hypertension, and this relationship is independent of traditional risk factors.

Keywords:
ischemic heart disease, hypertension, uric acid, hyperuricemia

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Introduction

Cardiovascular diseases (CVDs) are a set of multiple disorders of the heart and blood vessels, including coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis, and pulmonary embolism [1].

It is clear that reducing the burden of cardiac diseases depends on early identification of its risk factors. There are various risk factors involved for CVDs, including family history, sex, race, age, hypertension, hypercholesterolemia, diabetes mellitus, obesity, smoking, and stress. Several recent experimental and epidemiological studies have reported an association between elevated levels of serum uric acid (SUA) and the risk of CVDs [2].

The most important study of a representative sample of the entire US population was the First National Health and Nutrition Examination Survey (NHANES 1), which found that increased SUA levels were independently and significantly associated with risk of cardiovascular mortality among men and women, over an average 16.4 years of follow-up. However, it has not been definitively established whether SUA is merely a marker for risk or a causative agent in CVD, or whether treatment targeting SUA levels affects outcomes [3].

Patients and methods

This is a cross-sectional study conducted in Assiut University Hospitals, Faculty of Medicine, Assiut University, Egypt, in the period from January 2017 to December 2017. The study was conducted after approval from the Ethical Committee of Faculty of Medicine. A total of 40 patients were included in the study after an informed consent.

Inclusion criteria

Patients admitted to our hospital with primary hyperuricemia with SUA level greater than 7.0 mg/dl in men and greater than 6.0 mg/dl in women in the absence of the secondary causes of elevation of SUA, aged 18 years or older, were included [4].

Exclusion criteria

Diabetics; patients with chronic kidney disease; patients on diuretics for any cause; patients with any hematological abnormalities like hemolytic anemia, leukemia, or other myeloproliferative disorder; and patients on medications causing secondary hyperuricemia such as cyclosporine and aspirin were excluded.

A detailed history and thorough clinical examination was carried out in each patient, with special concern paid to the following:

(1) Blood pressure (BP) measurement was performed according to WHO guidelines [5].
(2) BMI was calculated by dividing weight in kilograms by the square of height in meters. Normal weight was defined as 18.5 kg/m^2–24.9 kg/m^2.
(3) Laboratory investigations: a blood sample was collected for the laboratory assessments, which included SUA, random glucose level, complete blood count, liver function tests (aspartate transaminase, alanine transaminase, and albumin), and creatinine levels. The glomerular filtration rate was also calculated through the Cockroft–Gault formula (140 – age × weight/creatinine × 72 for men and for women, multiplied by the correction factor of 0.85) [6]. Total cholesterol, high-density lipoprotein cholesterol, triglycerides, and low-density lipoprotein cholesterol were also assessed. Hyperuricemia was defined as SUA greater than 7.0 mg/dl for men and SUA greater than 6.0 mg/dl for women [4].

12-lead ECG

A 12-lead standard resting ECG was performed in all patients during the hospital stay to detect ischemic changes (depressed or raised ST-segment and/or T-wave changes) and the diagnosis of left ventricular hypertrophy.

Echocardiography

All patients received transthoracic full echocardiographic examinations. Complete M-mode, 2-dimensional, and Doppler echocardiography was performed. Grading of regional myocardial function depended on the quality of contraction: normal, hyperkinetic, hypokinetic, kinetic, or dyskinesia.

Statistical analysis

The data were tested for normality using the Shapiro–Wilk test and for homogeneity variances before further statistical analysis. Categorical variables were described by number and percentage, whereas continuous variables were described by mean, SD, and median. χ^2-test and Fisher's exact test were used to compare between categorical variables, where comparison between continuous variables was done by *t*-test for normally distributed data and Mann–Whitney *U*-test for abnormally distributed data. A two-tailed *P* value less than 0.05 was considered statistically significant.

Results

All of the studied patients had normal abdominal ultrasonographic findings with normal urine analysis.

None of the patients were known to be diabetic, hypertensive, or smoker. Moreover, none of them had gout, kidney diseases, or liver cirrhosis (Tables 1).

Laboratory data of the studied patients

Full laboratory data are summarized in Table 2. It was noticed that all studied patients had normal laboratory range of the tests.

Level of serum uric acid in the studied patients

All studied patients had SUA above 7 mg/dl. Mean ± SD of serum acid was 9.95 ± 2.67 mg/dl, with range between 7 and 18 mg/dl (Table 3).

Frequency of hypertension and ischemic changes on echocardiography in the studied patients

It was shown that of 40 studied patients in the study, 15 (37.5%) patients were discovered to be hypertensive and 13 (32.5%) patients had ischemic changes on echocardiography (Table 4).

Serum uric acid in patients with high blood pressure and patients with normal blood pressure

It was noticed that SUA was significantly higher in patients with high BP in comparison with patients with normal BP (10.26 ± 2.91 mg/dl in patients with high BP vs. 8.84 ± 1.59 mg/dl in patients with normal BP; $P = 0.04$) (Table 5).

Serum uric acid in patients with ischemic heart disease and patients without ischemic heart disease

It was noticed that SUA was significantly higher in patients with ischemic heart disease (IHD) in comparison with patients without

Table 1 Demographic data of the studied patients. It was noticed that all of the included patients had normal BMI

	N=40
Age (years)	
Mean±SD (range)	56.15±16.25 (23-87)
Sex [*n* (%)]	
Male	25 (62.5)
Female	15 (37.5)
Body weight (kg)	66.77±7.58
Height (cm)	163.12±5.19
BMI (kg/m²)	23.81±1.29

Table 2 Laboratory data of the studied patients

Parameters	Mean±SD
Complete blood picture	
Hemoglobin (g%)	13.52±1.42
Total leukocytic count (×10³/l)	8.91±2.96
Platelets (×10³/l)	258.87±98.06
Kidney functions	
Urea (µmol/l)	6.36±2.92
Creatinine (mmol/l)	91.15±25.48
Liver function tests	
Total bilirubin (mmol/l)	1.08±0.02
Direct bilirubin (mmol/l)	0.35±0.01
Aspartate transaminase (U/l)	25.55±6.67
Alanine transaminase (U/l)	26.02±5.09
Serum albumin (mg/dl)	37.50±4.65
Random blood sugar (mmol/l)	5.01±0.55
International randomized ratio	1.05±0.06
Cholesterol (mg/dl)	121.62±30.72
Triglyceride (mg/dl)	89.32±23.12

Data were expressed in the form of mean and SD.

Table 3 Level of serum uric acid in the studied patients

	Male (*n*=25)	Female (*n*=15)	Total (*n*=40)
Serum uric acid (mg/dl)			
Mean±SD	9.75±2.39	10.26±3.18	9.95±2.67
Range	7.3-13.4	7-18	7-18

IHD (11.20 ± 3.61 mg/dl in patients with IHD vs. 9.34 ± 1.78 mg/dl in patients without IHD; $P = 0.03$) (Table 6).

Presence of hypertension and ischemic heart disease in relation to serum uric acid level

It was noticed that presence of high BP and ischemic changes in echocardiography was higher with higher levels of SUA in the studied patients (Fig. 1).

Correlation of serum uric acid with other parameters in the current study

SUA had a strong positive significant correlation with systolic BP and diastolic BP [r (P)=0.91 (0.00) and 0.78 (0.00), respectively], whereas correlations of uric acid with other variables were insignificant ($P < 0.05$) (Table 7, Figs 2 and 3).

Table 4 Frequency of hypertension and ischemic changes on echocardiography in the studied patients

	Female (*n*=15)	Male (*n*=25)	Total (*n*=40)
Hypertension	6 (40)	9 (36)	15 (37.5)
Ischemic changes	6 (40)	7 (28)	13 (32.5)

Data were expressed in the form of frequency (%).

Table 5 Serum uric acid in patients with high blood pressure and patients without normal blood pressure

	With high blood pressure (*n*=15)	With normal blood pressure (*n*=25)	*P*
Serum uric acid (mg/dl)	10.26±2.91	8.84±1.59	0.04

Data were expressed in the form of mean±SD. $P<0.05$, significant.

Table 6 Serum uric acid in patients with ischemic heart disease and patients without ischemic heart disease

	With ischemic heart disease (*n*=15)	Without ischemic heart disease (*n*=25)	*P*
Serum uric acid (mg/dl)	11.20±3.61	9.34±1.78	0.03

Data were expressed in the form of mean±SD. $P<0.05$, significant.

Table 7 Correlation of serum uric acid with diastolic blood pressure and systolic blood pressure

	r (*P*)
Age	–0.1 (0.87)
Systolic blood pressure	**0.91 (0.00)**
Diastolic blood pressure	**0.78 (0.00)**
BMI	–0.14 (0.33)
Blood urea nitrogen	0.22 (0.14)
Serum creatinine	–0.01 (0.21)
Triglyceride	–0.43 (0.32)
Cholesterol	–0.23 (0.35)

r indicated to strength of correlation, whereas *P* indicated significance of correlation, which is considered significant if<0.05. Bold: Serum uric acid had strong positive significant correlation with SBP and DBP (r (*P*) = 0.91 (0.00) and 0.78 (0.00)) while correlations of uric acid with other variables were insignificant ($P< 0.05$).

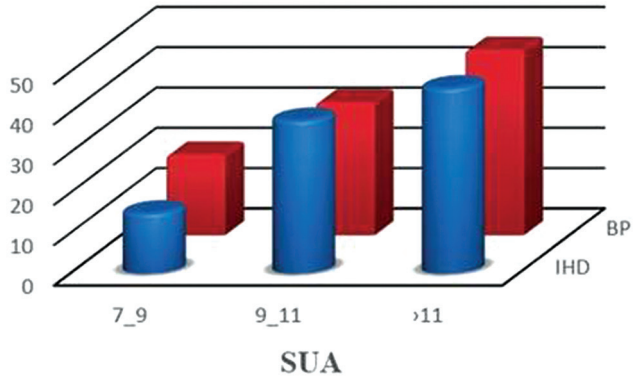
Discussion

The uric acid has several biological properties that can be either beneficial or detrimental. SUA is a powerful antioxidant, and it protects against free radical damage. Along with ascorbate, SUA accounts for up to 60% of the serum free radical scavenging capacity [7].

SUA levels can be measured at low cost in almost all hospitals in the world, especially in developing countries, where many hospitals have no facilities to measure other expensive prognostic markers such as high sensitive C-reactive protein, brain natriuretic peptide, interleukin-6, and many others as indicators of CVD.

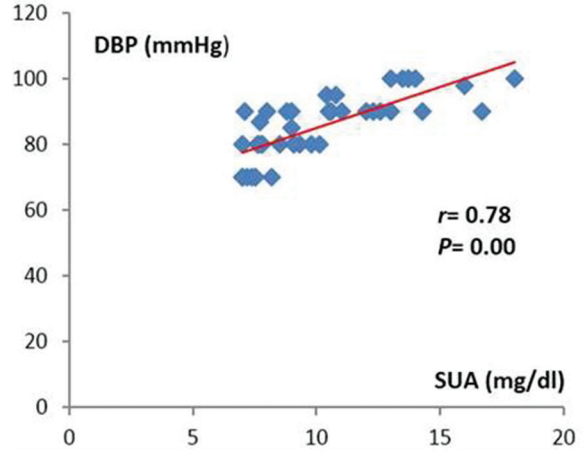
Previous studies have demonstrated that SUA is associated with CVD in high-risk populations, including patients with metabolic syndrome, hypertension, diabetes, hyperlipidemia, congestive heart failure, and stroke [8–11].

Figure 1



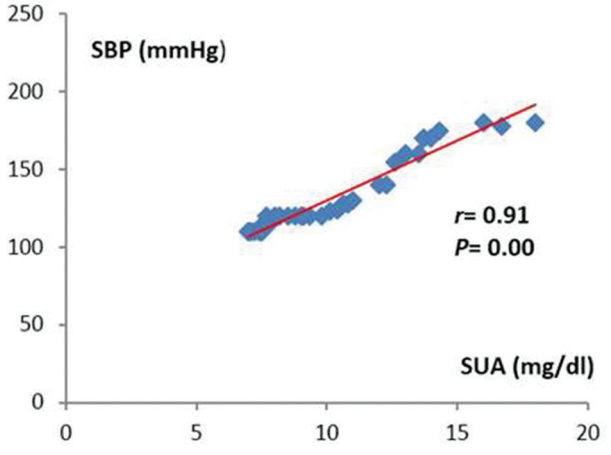
Increasing occurrence of hypertension and IHD with increasing levels of SUA. BP, blood pressure; IHD, ischemic heart disease; SUA, serum uric acid.

Figure 2



Correlation between serum uric acid (SUA) and diastolic blood pressure (DBP).

Figure 3



Correlation between serum uric acid (SUA) and systolic blood pressure (SBP).

Our study is the first in Egypt to handle this association after controlling for a wide range of traditional risk factors such as smoking, diabetes mellitus, HTN, dyslipidemia, kidney affection, anemia, diuretic use, and obesity.

In our study, we found that increased uric acid level was an independent risk factor for the presence of ischemic events by echocardiography. Our main observation is supported by the National Health and Nutrition Examination Survey (NHANES) [3], which found an independent association of SUA with CVD, but contradicts other studies such as an analysis of the Framingham Heart Study[12] which reported an absence of an independent association after adjusting for a number of traditional CVD risk factors, with a substantial contribution of diuretic use to the nonsignificance of SUA for the prediction of cardiovascular morbidity and mortality. In the present study, although we excluded diuretic use as well as a wealth of traditional CVD risk factors, the association of SUA with CVD was still maintained.

Moreover, in the study carried out in 2013 by Kivity *et al.* [13], in 9139 healthy adults, with a mean 4.8-year follow-up, the hazard ratio for CVD, adjusted for age, serum creatinine level, BMI, systolic BP, low-density lipoprotein cholesterol level, triglyceride level, plasma fasting glucose, physical activity, cardiovascular family history, use of diuretics, and current smoking, was 1.24 (95% confidence interval: 1.08–1.41) and supported SUA as a marker of CVD risk in healthy populations [13].

In addition, more and more studies have revealed independent associations in various populations, as shown in the Multiple Risk Factor Intervention Trial (MRFIT) study [10], the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) Study [8], the Vorarlberg Health Monitoring and Promotion Program [14], and in studies of Chinese[15] and Japanese cohorts [16].

In addition, several clinical studies link SUA to coronary artery disease, such as a report from Saito [17] and colleagues showing a correlation of SUA with lipid-rich coronary plaques, a composition known to be a precursor of future cardiac events. Similar findings have been reported for carotid plaques [18]. Moreover, SUA has been linked to the extent of coronary atherosclerosis, reduced coronary flow reserve, and impaired coronary microvascular function. A recent study published by Pagidipati *et al.* [19], including the PLATO and TRACER study populations, could demonstrate a significant association of SUA with short-term adverse outcome independent of the presence of gout.

Recently, another study carried out by Chang *et al.*[20] in Taiwan, investigated the association

between SUA concentration and cardiovascular risk. This study prompted earlier surveillance of the SUA level in asymptomatic individuals and resulted in the identification of populations at high risk of CVD [20].

Our study did not determine the underlying mechanisms regarding the role of SUA in the development of CVDs; however, other research groups have proposed possible mechanisms. Intracellularly and in mitochondria, uric acid has been shown to release free radicals and induce oxidative stress, resulting in enhanced atherosclerosis [21]. SUA might also induce vascular inflammation by stimulating the expression of chemokines, such as monocyte chemoattractant protein-1 [22]. SUA also has been significantly and independently associated with the levels of C-reactive protein, interleukin-6, interleukin-18, and tumor necrosis factor-α. Furthermore, SUA has been shown to be associated with a reduction in nitric oxide availability causing endothelial dysfunction [23].

Moreover, according to our results, SUA is not only significantly associated with IHD ($P < 0.05$) but is also positively and significantly associated with HTN.

Hypertension is probably the most important risk factors for CVD and affects a large percentage of the population worldwide. Thus, among the priorities for CVD prevention, the detection and correction of all the reversible causes of uncontrolled BP can play a major role.

From this study, it can be observed that there were higher means of BP at the highest levels of SUA, which corresponds to the results found in 2006 by Perlstein *et al.* [24], in 2062 individuals, over a 21-year period, where arterial hypertension was also associated with higher quintiles of SUA.

In 2016, a study of 26 442 Japanese males aged 18–60 years free from hypertension or diagnosed CVD at baseline concluded that high SUA level was associated with future hypertension in young and middle-aged Japanese males. This association was stronger among patients 40 years or older [25].

A recent study published in 2018 evaluated a total of 2335 Japanese male workers without hypertension who ranged in age from 18 to 64 years at a worksite. These men were followed for 6 years. SUA levels were associated with the future incidence of hypertension, and the association was observed in the younger individuals, those without diabetes, and those with preserved high-density lipoprotein cholesterol levels [26].

The biological explanation for this fact is supported by studies carried out with animal models such as rats, which showed the development of arterial hypertension after the induction of hyperuricemia, caused by a probable decrease in nitric oxide in the renal macula densa and by direct stimulation of the renin–angiotensin system, with both mechanisms causing vasoconstriction and therefore, BP increase [27].

Our results are of interest as SUA is easily assessed and represents a treatable target. Early trials already have suggested a benefit of lowering SUA with allopurinol on endothelial dysfunction, carotid intimal thickness, angina in patients with stable coronary artery disease, ventricular hypertrophy, arterial stiffness, and progression of chronic kidney disease [28]. Although it has been argued that this might be owing to a sole inhibition of xanthine oxidase, a recent study also showed a benefit using probenecid in lowering BP, such as a uricosuric. This points toward an independent pathophysiological role of SUA. Currently, the ALLHEART study, investigating the benefit of allopurinol as addition to secondary prevention therapy, is recruiting, but results are not expected to be available before 2020 [29].

The association of uric acid with CVD is indisputable, given that uric acid is associated with CVD risk factors, such as diabetes and hypertension. Whether uric acid is independently associated with CVD remains unresolved. Moreover, the evidence of an independent role for uric acid, at least in some populations, does not indicate causality. Less obvious is the possibility of causality, even without an independent relation. The Framingham Heart Study [12], and more recently Panero *et al.* [30], concluded that uric acid was not a causal risk factor for cardiovascular events, because it was not independent of hypertension. However, if uric acid causes hypertension, and hypertension causes CVD, then uric acid has a causal role in CVD, even if it does not show independence from hypertension when evaluated as a risk factor for CVD.

Recommendations

We recommend the following:

(1) Clinical practice still needs further clinical trials finalized to assess urate-lowering efficacy in the much more global context of cardiovascular prevention.
(2) Elevations of uric acid more than 6 mg/dl should be considered a ‘red flag’ in those patients at risk for CVD and should alert the clinician to strive to utilize a global risk reduction program in a team effort to reduce the complications of the atherogenic process resulting in the morbid–mortal outcomes of CVD.

Conclusion

There is a strong and significant association between high uric acid levels and IHD. Moreover, uric acid is strongly and positively associated with hypertension, and this relationship is independent of clinical risk factors. As SUA is an easily accessible and inexpensive biomarker, identification of hyperuricemia as a cause rather than a consequence of subclinical atherosclerosis might be a potentially useful monitoring tool and therapeutic target for future CVD.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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