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Prothrombotic Effect of Serum Uric Acid in Hypertensive Patients

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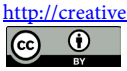

Abstract

Aim: The purpose of this study was to investigate the possible relationship of serum uric acid levels (SUA), in hypertensive patients treated or not, with blood clotting factors. **Design and Methods:** The study population consisted of 1297 hypertensive patients (46% men) treated (53%) or newly diagnosed untreated (mean age 57.8 years, mean office systolic/diastolic blood pressure –Ms/DBPo-: 147.9/91.6 mmHg, mean office heart rate –mHRo-: 75 ± 11.1 beats per minute, mean body mass index-Mbmi-: 28.2 ± 4.9 kg/m^2, mean waist/hip ratio –Mw/H-: 0.88 ± 0.84 In the aforementioned patients SUA and blood clotting factors were measured, such as fibrinogen, international normalized ratio (INR) and serum homocysteine (Hcys). Moreover in a subgroup (N = 323) of the above mentioned study population, 323 patients, blood antithrombin III (ATIII), and D-dimers were also measured. Finally, in a small subgroup (N = 42) of the above mentioned study population of 42 patients, blood plasminogen activator inhibitor-1 (PAI-1) was measured. Values obtained were interrelated with Pearson correlation. **Results:** The following significant correlations were observed: SUA vs fibrinogen ($r = 0.164$; $p < 0.001$), SUA vs INR ($r = 0.061$, $p = 0.029$), SUA vs Hcys ($r = 0.257$, $p < 0.001$), SUA vs AT III ($r = -0.163$, $p = 0.021$), SUA vs D-dimers ($r = 0.120$, $p = 0.046$ and SUA vs PAI-1 ($r = 0.349$, $p = 0.034$). Moreover, Regression analysis showed that uric acid level was independently associated with fibrinogen, INR, Hcys, ATIII, D-dimers and PAI-1 ($p < 0.005$). **Conclusions:** In hypertensive patients, SUA levels correlate significantly with blood clotting factors, possibly suggesting a prothrombotic effect of SUA in those patients.

Subject Areas

Cardiology, Hematology, Metabolic Sciences

Keywords

Hypertension, Uric Acid, Blood Clotting Factors, Pro-Thrombotic Factors

1. Introduction

Uric acid is the final product of purine nucleotide catabolism. Hypoxanthine and xanthine are the intermediate products of this catabolism. Xanthine oxidoreductase catalyzes the final two reactions in the biochemical chain that leads to uric acid formation: the conversion of hypoxanthine to xanthine and xanthine to uric acid. In most mammals, uricase (urate oxidase), an enzyme very effective in lowering uric acid levels, oxidizes uric acid to allantoin which is highly soluble in water and excreted unchanged in the urine [1]. However, during the Miocene epoch, two parallel but distinct mutations occurred in early hominoids that rendered the uricase gene nonfunctional [2]. As a consequence, humans and the great apes have higher uric acid levels, 3 to 10 times higher compared with most mammals (1 - 2 mg/dL).

Uric acid levels also vary significantly within humans as the result of factors that increase generation (such as high purine or protein diets, alcohol consumption, conditions with high cell turnover, or enzymatic defects in purine metabolism) or decrease excretion. A reduction in glomerular filtration rate (GFR) increases serum uric acid, although a significant compensatory increase in gastrointestinal excretion occurs [3]. Hyperuricemia also may result from increased net tubular absorption. After filtration, uric acid undergoes both reabsorption and secretion in the proximal tubule, and this process is mediated by a urate/anion exchanger and a voltage sensitive urate channel [4] [5]. Organic anions such as lactate decrease urate secretion by competing for urate through the organic anion transporter, whereas several substances, have opposite effects [6]. Hyperuricemia is defined as blood uric acid levels above the normal reference interval. Generally, hyperuricemia in adults is defined as a blood uric acid concentration greater than 7.0 mg/dL in men and 6.0 mg/dL in women [7].

The relationship between uric acid and arterial hypertension was originally described in the early 60s, when prospective studies revealed that 26% of untreated hypertensive patients with normal renal function had elevated plasma uric acid levels. This outline increased to 58% for those receiving antihypertensive drugs, and it was principally high in those taking diuretics (70%) [8]. The association is independent of elements of the metabolic syndrome, alcohol intake, and renal function [9]. It remains unresolved whether the association of hyperuricemia with hypertension is solely because of underlying renal and metabolic abnormalities. Decreased renal blood flow and decreased tubular secretion of uric acid have been associated with hyperuricemia in hypertension [10] [11]. Uric acid is thought to play a pathogenic role in hypertension [12] [13] [14] mediated by several mechanisms such as inflammation, vascular smooth muscle

cell proliferation in renal microcirculation, endothelial dysfunction and activation of the rennin-angiotensin-aldosterone system [15] [16]. Animal models have shown that acute elevations of serum urate, by inhibition of uricase, induce a prompt rise in blood pressure and that chronic urate elevation maintains the rise in pressure and induces irreversible vascular damage and glomerular changes and results in a form of salt-sensitive hypertension [17] [18].

A relationship between hyperuricemia and cardiovascular (CV) disease has been established since the 1900s [19]. Multiple studies have associated elevated serum uric acid with the precursors of CV diseases, including hypertension, metabolic syndrome (MetS) [20] [21] and coronary artery disease, as well as with closely related vascular diseases such as cerebrovascular disease, vascular uric acid dementia, preeclampsia and kidney disease [22]. There are data suggesting that increased SUA levels are independently and significantly associated with risk of CV mortality [23]. Several pathophysiological mechanisms have been postulated including multiple proatherogenic processes, increased oxidative stress [24] [25], vascular smooth muscle cell proliferation, leukocyte activation, stimulation of the inflammatory pathway, possible prothrombotic effects mediated by platelet adhesiveness and aggregation and crystal formation within coronary atherosclerotic plaques [26] [27]. In addition, uric acid has proved to be an excellent marker for tissue ischemia and endothelial dysfunction [28] [29], and it has been shown to play a role in the development of atherosclerotic lesions [30] [31] [32].

Uric acid has long been known to be a CV risk factor. Recently, a close association between elevated uric acid and numerous markers of inflammation has been noticed, such as white blood cells [33]. What is more, uric acid has also been shown to directly stimulate the production of inflammatory mediators, such as CRP, in vascular cells [34]. These findings suggest that uric acid is an actual endothelium-injuring factor. Given the association between uric acid and the formation of CRP presented above one cannot ignore its significance as a potential indirect prothrombotic factor. There are few data demonstrating the direct association between uric acid and the markers of prothrombotic state, but high uric acid levels should be a link between endothelial dysfunction, pro-inflammatory and pro-thrombotic states and could be a possible independent risk factor for VTE, as some clinical studies suggest [35] [36] [37] [38] [39].

Thus, the present study aims to define the correlation between serum uric acid levels and blood clotting factors in a special population, namely hypertensive individuals, treated or newly diagnosed untreated, in an attempt to clarify the existence of uric acid either as a marker with predictive value or as a marker of thrombotic process among hypertensive individuals.

2. Material and Methods

2.1. Patient Population

We studied 1297 hypertensive patients (45.9% male) of mean age 57.8 years, treated (53%). Or newly diagnosed never-treated with anti-hypertensive drugs,

who were self-referred to our outpatient cardiology hypertensive clinic, for blood pressure evaluation. Patients were excluded from the study, if they suffered from any CV disease, secondary hypertension and any other clinically significant concurrent medical condition such as thyroidal, psychiatric, neuromuscular, chronic kidney disease, respiratory, hepatic or gastrointestinal illness or systemic disease. None of the participants had any history or clinical/laboratory evidence of recent infection, inflammation or underwent any medical treatment (including anti-inflammatory treatment and hormone replacement therapy) the last month before entry into the study. Patients under treatment for hyperuricemia or any anticoagulant therapy, were also excluded from the study. The study was approved by our hospital's ethics committee and conformed to the 1964 Declaration of Helsinki. All subjects gave their written informed consent at the baseline of our study.

2.2. Measuring Study Variables

In the first visit resting sitting, BP was measured twice with at least 5 minute intervals using an automatic sphygmomanometer. If the difference between the first and second measurement was more than 10 mmHg, then repeated measurements were performed. The average of the last two measurements was used for screening. Subsequently BP measurements were made in our outpatient clinic according to the recent guidelines, at three separate visits with a mean elapsing time of 1 week. In each visit, participants were encouraged to relax for almost 10 minutes and subsequently in a quiet room with a stable temperature and luminosity, an experienced cardiologist after having explained the procedure to the participants, performed three different BP measurements at 5-minute intervals by using a mercury sphygmomanometer. Korotkoff phase 1 and 5 were used to determine SBPo and DBPo, respectively in each visit, the second and third BP measurements were averaged and the final office BP, consisted of the mean of the three visits. Furthermore, on the first visit a bilateral measurement was performed to define the arm subjected to the relatively higher haemodynamic load and accordingly was used for all the following measurements.

The anthropometric variables were measured according to the written protocol. Weight, height, waist circumference and hip circumference were measured (WC was measured on a horizontal plane midway between the inferior margin of the ribs and the superior border of the iliac crest using a tape measure). The values of BMI were calculated from the following formula: BMI = [W(kg)/h^2 (m)]. The WHR was calculated form the following formula: WHR = waist circumference [cm]/hip circumference [cm]. Blood veinal samples were collected from all participants for the determination of serum uric acid (SUA) as well as plasma urea and creatinine, using enzymatic methods. Blood clotting factors were measured, such as: blood fibrinogen and international normalized ratio (INR) of prothrombin time were measured in the total study population (N = 1297). Blood antithrombin III (ATIII), serum homocysteine (HCy) and D-dimers

were measured in an smaller number of participants (N = 323) and finally in N = 42 study patients, plasminogen activator inhibitor-1 (PAI-1) Enzyme-Linked Immunosorbent Assay (ELISA) was measured as well.

2.3. Statistical Analysis

Continuous variables are presented as either mean (±standard deviation) or medians (interquartile range) and categorical variables as numbers and percentages as appropriate. Correlation analyses were performed using Pearson's correlation coefficient. Multivariable regression analysis was used to examine the relation between serum uric acid and blood clotting factors, after adjustment for confounding factors. Statistical significance was set at p value < 0.05. Results were analyzed with SPSS for Windows software.

3. Results

The clinical and laboratory characteristics of patients are shown in Table 1.

Table 1. Clinical and laboratory characteristics of patients population.

	Study Population (N = 1297)
Age (years)	57.8 ± 13.5
Female sex (%)	54
BMI (kg/m^2)	28.2 ± 4.9
Waist/Hip ratio	0.88(0.82 - 0.94)
SBPo (mmHg)	147.8 ± 20.4
DBPo (mmHg)	91.6 ± 13
HRo (b/1')	75.3 ± 11.1
Treated (%)	53
Serum Uric Acid (mg/dl)	5.18 ± 1.6
Urea (mg/dl)	39.06 ± 16.5
Serum Creatinine (mg/dl)	1.07 ± 5.65
eGFR (ml/min)	81.7 ± 35.7
Fibrinogen (mg/dl)	347.9 ± 98.9
INR	1.07 ± 0.5
Hcys (mcmol/L)	13.9 ± 6.7
D-Dimers (ng/mL)	272.1 ± 50
ATIII (%)	131.7 ± 73.11
PAI-1 (ng/mL)	6.05 ± 6.1

SBPo: Systolic Blood Pressure at office, DBPo: Diastolic Blood Pressure at office, HRo: Heart Rate at office, BMI: body mass index, e-GFR: estimated-Glumerular Filtration Rate (Cockcroft Gault Formula).INR: international normalized ratio of prothrombin time, PAI-1: plasminogen activator inhibitor-1, Hcys: Homocysteine, ATIII: *Antithrombin III.*

Moreover, correlation between SUA levels and blood clotting factors are shown in Table 2.

It is evident from Table 2, that all the studied clotting factors are significantly correlated with SUA

Furthermore, it seems that fibrinogen, INR, Hcys, D-dimers and PAI-1exhibit a positive correlation with SUA levels, among hypertensive patients, while ATIII exhibit a negative correlation with SUA levels Multivariable regression analysis revealed that fibrinogen, Hcys, D-dimers are independent predictors of uric acid (Table 3).

4. Discussion

In the present study, we evaluated the relationship between the SUA levels, with various parameters indicative of clotting factors in a large cohort of 1297 hypertensive patients (45.9% male) of mean age 57.8 years, treated (53%), or newly diagnosed never-treated with anti-hypertensive drugs, or any anticoagulant therapy. Serum uric acid (SUA), as well as blood clotting factors were measured, such as: blood fibrinogen and international normalized ratio (INR) of prothrombin time in the total study population (N = 1297), blood antithrombin III(ATIII), serum homocysteine (Hcys) and D-dimers were measured in an smaller number of participants (N = 323) and finally in N = 42 study patients, plasminogen activator inhibitor-1 (PAI1) Enzyme-Linked Immunosorbent Assay (ELISA) was measured as well.

We found in the overall study hypertensive population, a significantly positive correlation between SUA levels with blood fibrinogen and international normalized ratio (INR) of prothrombin time, a significantly correlation between SUA levels negative with blood AT III, (as was expected), positive with serum Hcys and D-dimers,when were measured in an smaller number of participants (N =

Table 2. Correlations between serum uric acid and blood clotting factors in overall study population (N = 1297).

	r	p value
Fibrinogen	0.164	<0.001
INR	0.061	0.029
(a) Correlations between serum uric acid and blood clotting factors in sub study population (N = 323)		
HCys	0.257	<0.001
ATIII	−0.163	0.021
D-dimers	0.133	0.043
(b) Correlations between serum uric acid and blood clotting factors in a smaller study population (N = 42)		
PAI 1	0.362	0.018

Hcy: Homocysteine, ATIII: Antithrombin III, PAI-1: plasminogen activator inhibitor-1.

Table 3. Regression (unadjusted or adjusted for age and sex) analysis with serum uric acid levels as the dependent variable in the study population as well as in the substudies.

	b coefficient*	95% confidence interval	p value	b coefficient**	95% confidence interval	p value
Fibrinogen	0.003	0.002 - 0.004	<0.001	0.002	0.001 - 0.003	<0.001
INR	0.069	−0.147 - 0.286	NS	0.037	−0.179 - 0.253	NS
HCys	0.062	0.042 - 0.082	<0.001	0.062	0.042 - 0.009	<0.001
ATIII	−0.002	−0.005 - 0.001	NS	0.002	−0.004 - 0.028	NS
D-dimers	0.000	0.000 - 0.001	0.043	0.012	−0.000 - 0.001	NS
Pai1	0.019	−0.002 - 0.041	NS	0.019	−0.003 - 0.040	NS
	b coefficient* **	**95% confidence interval**	**p value**			
Fibrinogen	0.004	0.003 - 0.005	<0.001			
INR	0.070	−0.136 - 0.276	NS			
HCys	0.040	0.020 - 0.060	<0.001			
ATIII	−0.002	−0.005 - 0.001	NS			
D-dimers	0.001	0.000 - 0.001	0.022			
Pai1	0.010	−0.009 - 0.028	NS			

In all groups of the study population, unadjusted or adjusted for sex and age, two of the biochemical parameters were independent predictors of SUA levels, fibrinogen and Hcys while D-dimers in the unadjusted analysis was independent predictor of the SUA levels did not remained statistically significant after adjusting for age as independent predictor of SUA levels, while adjusted for sex remained independent predictor for SUA levels (Table 3), meaning that age eliminates the significant correlation of D-dimers. PAI-1, INR and ATIII were not independent predictors of SUA levels in this regression analysis.

323 subgroup) and finally in a significantly positive correlation between SUA levels and PAI1 in N = 42 study patients.

The regression analysis with SUA as independent variable (in the above mentioned groups), revealed that blood fibrinogen and serum Hcys were independent predictors of SUA levels (Table 3) and remained after adjusting for age and sex, while D-dimers was independent predictor of SUA levels only in unadjusted regression analysis, as well as in the adjusted for sex, meaning that age influences the predictor value of this parameter, on SUA levels.

Finally, blood INR, ATIII and PAI1 were not independent predictors of SUA levels in the above hypertensive population, meaning that other cofounders interfere in the correlation, between SUA levels and these parameters and eliminated the significance of this.

Many researchers, investigated years ago, the association of increased SUA levels and thrombosis, as in 1955 Mengghini P and Bellotti R found a correlation between thrombophlebitis in young patients with hyperuricemia and SUA levels [40].

In 1972, Frank J. Viozzi, and colleges [41] found in gout patients, an association between SUA levels and arterial thrombosis, which attributed to the plate-

lets hyperactivity that may explain the increased risk of myocardial infarction before the age of 50 years old, in patients with primary gout.

Subsequent studies suggested the contribution of hyperuricemia to CV disease risk, independently of traditional CHD risk factors, with a more pronounced increased risk for CHD mortality in women [42], based on patho-physiological mechanisms including inflammation, vascular smooth muscle cell proliferation and platelet adhesiveness and aggregation [43]. The persistent inflammation anywhere in the body can promote prothrombotic environment in which the fibrinogen, as well as other inflammatory parameters, may play crucial role in the atherosclerotic process [44].

Hyperuricemia is nowadays an established cardiovascular risk factor [4] [8] [13] and contributes in the onset of CVD via many mechanisms, as endothelial dysfunction (mediated by ROS, resulting in inflammation of the vascular endothelial cells and proliferation of vascular smooth muscle cells) [45] and prothrombotic state, driven by vascular endothelium injury, which is one of the initial triggers incriminated in clotting formation, in the context of hypercoagulability, inflammation and endothelial injury that finally may promote venous thrombosis, recurrent cases of venous thromboembolism, independent of other confounding risk factors, or increased risk for pulmonary embolism, while in the context of plaque hypoxia, inflammation and oxidative stress may lead to atherothrombosis [46] or to instability of the coronary plaques with increased CV mortality, The physiopathological relationship between hyperuricemia, CVD, cardiovascular risks, as hypertension, remains controversial and is still a subject of research and discussion.

Evidence promotes connection between elevated SUA levels and endothelium dysfunction (ED), inflammation, and prothrombotic state [47], as markers of pro-inflammatory state correlate with prothrombotic markers such as serum fibrinogen and platelet count, indicating an inflammation-dependent activation of the coagulation system physiologically across the coagulation cascade, promoting clotting, giving a more clear link between inflammation and atherosclerosis [35], but not between gout and deep vein thrombosis the mechanism and the causality of which, remain less clear despite the evidence from many studies, that support the association between gout and the risk of incidence deep vein thrombosis and prognosis, linking the preexistence of ED and the enhancement of thrombosis, via endothelin-1 and platelet activating factor that promote vasoconstriction, while, PAI1, tissue factor, von Willebrand factor, and Factor V promote thrombosis [48]. In another study elevated levels of Hcys, protein C-, protein S- or low levels of antithrombin and prothrombin G20210A variation denote to be risk factors for Venous thromboembolism [49].

But the question, despite and the recent study from Hongyin and colleges (2021), that suggest causative role of SUA and endothelial cells dysfunction, via TMEM16F [50], remains. Is SUA a factor or a marker for Venous Thromboembolism? [51]. In our study the independent and predictive association of fibrinogen levels, Hcys levels and D-dimers, as well as the correlation of INR, ATIII

and PAI1 with the SUA levels of hypertensive patients, may explain the atherosclerosis process of such patients, in between other known factors and the predisposition of these to develop and accelerate atherosclerosis may be a consequence of the combined effect of these two factors, inflammation and prothrombotic status. Cohen, E and colleges, in a recent retrospective cross-sectional analysis of data from a screening center in Israel assessing 16,477 subjects mean age: 46 years, found a significant association between hyperhomocysteinemia and hyperuricemia in males and females independently of the presence or not of hypertension, or the existence of gout [52] [53], linking these two factors in a common pathway, in the existence and influence of the methylenetetrahydrofolate reductase (MTHFR) enzyme that plays a role in both homocysteine and folate metabolism [54] [55]. In another study of Rosangela Spiga, and colleges 2017, about the association of uric acid with inflammatory biomarkers that induces inflammation via activating the NF-κB signaling pathway in HepG2 Cells, in a cohort of 2731 nondiabetic adults, they found a significantly positive association between SUA levels and fibrinogen and also the greater the levels of UA, the greater the levels of fibrinogen [56].

As concern as the results in our analysis, where, blood AT III, PAI1 and INR, were not independent predictors of SUA levels in the above hypertensive population, while they significantly correlated with SUA levels, may mean that other cofounders interfere in this correlation, that eliminated the significance of the predictive value. As it is well known conditions such as heredity conditions, liver synthesis, alcohol consumption, smoking, sex and age, may interfere with the level of ATIII [57], as the age interferes in the D-dimers level. The small group of patients with PAI1 measurement may explain these results.

5. Limitations

The major strength of our study was that we used a large sample size for measuring prothrombotic parameters in hypertensives (except the small group of PAI1) and we excluded the presence of secondary hypertension, CV disease, chronic kidney disease, malignancy, and any other medical treatment that could interact with thrombotic factors. Such data are very limited in the literature until today.

However, when interpreting our results, some limitations should be considered: all variables were measured once. Menopause status in women is not available and is known that there is an interaction between sex hormones, SUA levels (estrogens are uricosuric) and thrombotic status, as well as (post-menopause women are at higher risk).

Postmenopausal women have higher concentrations than age-matched premenopausal women and plasma concentrations of Hcys in postmenopausal women taking hormone replacement therapy are significantly lower than they are in those who do not take estrogen supplements, although, in our study Hcys remained a significant predictor factor of SUA levels even after adjusting for age

and sex, indicating the strong influence of Hcys, on SUA levels in hypertensives. Regular physical activity is associated with lower plasma fibrinogen levels in postmenopausal women; and finally, smoking status influences the thrombotic parameters as well [58] [59] [60].

Another limitation of our study is the small number of PAI 1 of treated or untreated hypertensive patients included in the study. Furthermore, we were not able to include some important confounders in this study, such as any dietary habits that influence the SUA levels. In summary, in our study, we have reported a significant correlation between thrombotic parameters and SUA levels in hypertensive treated or newly diagnosed untreated patients and some of them have a predictive value of uricemic status, underlining the importance of coexisting of inflammatory and thrombotic status in these patients.

Conflicts of Interest

The authors declare no conflicts of interest.

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