Effect of uric acid serum levels on carotid arterial stiffness and intima-media thickness: A high resolution Echo-Tracking Study

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Abstract

Serum uric acid (UA) has been shown to be a predictor of cardiovascular (CV) morbidity and mortality, and it may play a role in the pathogenesis of CV disease affecting vascular structure and function. However, there is limited evidence of its specific association with carotid artery stiffness and structure. The aim of our study was to evaluate whether UA is associated with early signs of atherosclerosis, namely local carotid arterial stiffness and intima-media thickening. We evaluated 698 consecutive asymptomatic patients, referred to the Cardiovascular Department for risk factors evaluation and treatment. All patients underwent carotid artery ultrasonography with measurement of common carotid intima-media thickness (IMT) and echo-tracking carotid artery stiffness index Beta.

Patients with hyperuricemia (defined as serum uric acid ≥7 mg/dL in men and ≥6 mg/dL in women) had higher IMT (0.97±0.22 *vs* 0.91±0.18, p<0.001) and stiffness index Beta (8.3±3.2 *vs* 7.5±2.7, p=0.005). UA levels correlated with both IMT (r=0.225; p<0.001) and stiffness index Beta (r=0.154; p<0.001); the correlations were statistically significant in males and females. In a multivariate model which included age, arterial pressure, serum glucose and LDL-cholesterol, serum UA emerged as an independent explanatory variable of IMT and stiffness index Beta. Carotid IMT and local arterial stiffness are related to UA independently of established CV risk factors; UA may play a role in the early development of atherosclerosis.

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Introduction

Serum uric acid (UA) has been reported to be a risk factor for kidney and cardiovascular diseases, including hypertension and coronary artery disease [1-4]. It was shown that UA could independently predict cardiovascular (CV) events [5-8]. However, the effective role of UA in the pathogenesis of atherosclerosis is unclear and still under debate. Some authors argue that the reported excess of CV events in the hyperuricemic population could be the result of factors that commonly accompany high UA levels, such as hypertension, hyperinsulinemia, and reduced glomerular filtration rate [9,10]. On the other hand, hyperuricemia has been linked to the arterial damage and left ventricular hypertrophy [11], which increase the risk of adverse CV outcomes.

Carotid artery intima-media thickness (IMT), measured by ultrasound, is among the first arterial wall anomalies that characterise the early phases of plaque formation. There is growing evidence that carotid IMT is associated with CV risk factors and CV disease. IMT is a strong predictor of CV events and is commonly endorsed for risk stratification [12-17]. Other arterial wall anomalies that have been extensively studied are the indices of arterial elasticity. Some studies have reported a reduced arterial compliance in patients (pts) with CV risk factors like hypertension, diabetes, and smoking [18,19]. Accordingly, several reports suggest that reduced arterial compliance predicts mortality and adverse outcome [20-21]. Carotid remodelling may be considered as an intermediate end-point to evaluate how hyperuricemia may enhance CV risk. However, little information is available on the role of UA on carotid artery structure and function in term of local artery stiffness.

In this study, we sought to evaluate the relationship between UA and subclinical carotid damage assessed by IMT measurement and an echo-tracking derived stiffness index, in a large cohort of 698 consecutive asymptomatic patients with CV risk factors.

Materials and Methods

Study population

A series of 698 consecutive asymptomatic patients were enrolled for a comprehensive risk factors evaluation. The evaluation consisted in recording a full medical history, physical examination, laboratory testing, assessment of CV disease risk, and carotid ultrasonography. Hypertension was defined as sustained elevation of blood pressure (BP) ≥140 mmHg systolic and/or ≥90 mmHg diastolic on at least 3 separate determinations obtained on different days or use of antihypertensive medications. Type 2 diabetes mellitus was defined as fasting serum glucose ≥126 mg/dl or use of antidiabetic medications. Obesity was considered as BMI ≥30 kg/m^2. Metabolic syndrome was defined according to the ATP III criteria [22]. Serum UA was measured by the uricase/peroxidase method. Hyperuricemia was defined as a serum UA ≥7 mg/dl in men and ≥6 mg/dl in women. Patients treated with allopurinol or febuxostat were excluded. All patients with a history of overt coronary artery disease, heart failure, cardiomyopathies and more than mild valvular disease were also excluded.

All patients signed informed consent for participation in this research.

Carotid ultrasonography

Trained sonographers performed high-resolution B-mode ultrasound imaging of the carotid arteries using a commercially available ultrasound system (ALOKA Alpha 10 system, Hitachi Medical Computer Systems Inc., Tokyo, Japan). Carotid arterial stiffness was estimated with carotid Beta index, calculated using the formula [23]: Beta index= ln(SBP/DBP)/(Ds x Dd/Dd), where SBP and DBP are systolic and diastolic BP, respectively; Ds and Dd are the systolic and diastolic diameters of the carotid artery.

These measurements were performed on the right common carotid artery with a high-resolution echo-tracking system. Carotid intima-media thickness (IMT) was measured in a longitudinal view, at the level of the far wall of the right common carotid artery, at 1 cm from the carotid bifurcation, in a region free of plaque [24].

Statistical analysis

Continuous variables were presented as mean values and standard deviations. Categorical variables are reported as frequencies and group percentages. Differences between hyperuricemic and normouricemic subjects were evaluated using the ANOVA test for continuous data and χ^2-test for categorical variables. Pearson's correlation analysis was used to assess the univariate correlations between UA levels, arterial stiffness index Beta and IMT. Multivariate linear regression analysis was carried out to evaluate the relationship between UA, IMT and arterial stiffness index Beta, independently from other CV risk factors. The level of statistical significance (p value) was set at 0.05. Data analysis was performed using SPSS version 19 (SPSS Inc., Chicago, IL, USA).

Results

A total of 698 subjects (age 57.3±13.7 years; 45.1% male; 19.5% with hyperuricemia) were included in the analysis. The main characteristics of the study population are reported in Table 1.

Table 1. Characteristics of the study population stratified by uric acid levels.

Characteristics	Total population N=698	Non-hyperuricemic N=562	Hyperuricemic N=136	p
Age (years)	57.3±13.7	57.1±14.0	58.0±12.4	0.509
Male sex (%)	45.1	44.7	47.1	0.341
Uric Acid (mg/dL)	5.3±1.3	4.9±1.0	7.2±0.8	<0.001
Index of stiffness Beta	7.7±2.8	7.5±2.7	8.3±3.2	0.005
Average IMT (mm)	0.92±0.19	0.91±0.18	0.97±0.22	<0.001
SBP (mmHg)	146±18	146±18	148±19	0.203
DBP (mmHg)	87±10	87±10	89±11	0.014
Total cholesterol (mg/dL)	223±46	222±45	230±47	0.048
LDL (mg/dL)	140±39	139±39	144±39	0.158
HDL (mg/dL)	54±14	54±14	51±13	0.005
Triglyceride (mg/dL)	150±92	142±82	187±122	<0.001
Glucose (mg/dL)	110±30	108±30	118±31	<0.001
Active Smoking (%)	12.6	13.7	8.1	0.081
Hypertension (%)	76.6	74.0	87.4	0.001
Dyslipidemia (%)	66.3	63.0	80.1	<0.001
Diabetes mellitus (%)	16.3	14.6	23.1	0.014
Obesity (%)	61.5	58.5	73.5	0.001

Values are expressed as average or as percentage. DBP, diastolic blood pressure; HDL, high density lipoprotein cholesterol; IMT, intima media thickness; LDL, low density lipoprotein cholesterol; SBP, systolic blood pressure.

In univariate analysis, UA showed a significant correlation with the carotid stiffness index Beta (r=0.154; p<0.001) and with carotid IMT (r=0.225; p<0.001). These correlations were statistically significant both in men and women (Figures 1 and 2).

Linear regression analysis demonstrated that UA levels were correlated with carotid IMT and stiffness index Beta independently of other CV risk factors (Tables 2 and 3).

Discussion

The hyperuricemic patients showed significantly higher values of stiffness index Beta and carotid IMT, indicating an early structural and functional damage of the carotid arteries in these patients. Moreover, we observed a linear relationship between serum UA and both IMT and carotid artery stiffness index Beta independently of other established CV risk factors in men and women. Carotid IMT and stiffness index Beta were best predicted by age in our study analysis. The SBP was positively correlated with carotid artery stiffness in women and IMT in men. The DBP was negatively related to the carotid artery stiffness; this is probably due to the fact that stiffness index Beta is calculated from pulse pressure which, given a certain SBP, is higher for lower values of DBP. The task of having a powerful marker of cardiovascular events in primary prevention represents an unquestionable benefit, and several studies have been already proposed with this aim [25,26]. The main limit of our study arises from the fact that the included

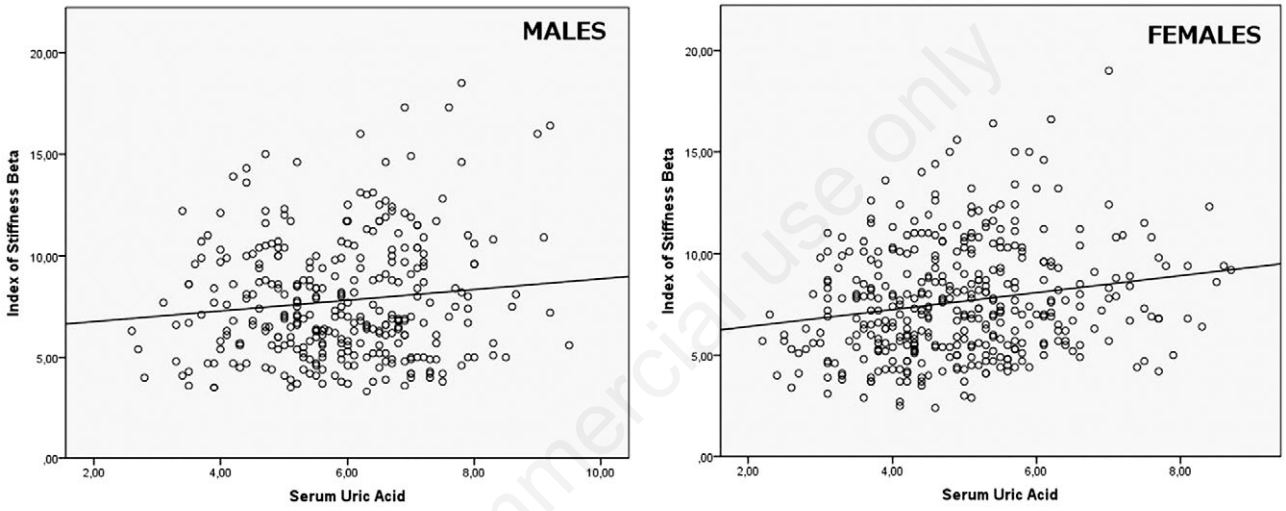

Figure 1. Relationship between serum uric acid (mg/dL) and index of arterial stiffness Beta in males (r=0.116; p=0.039) and females (r=0.190; p=<0,001).

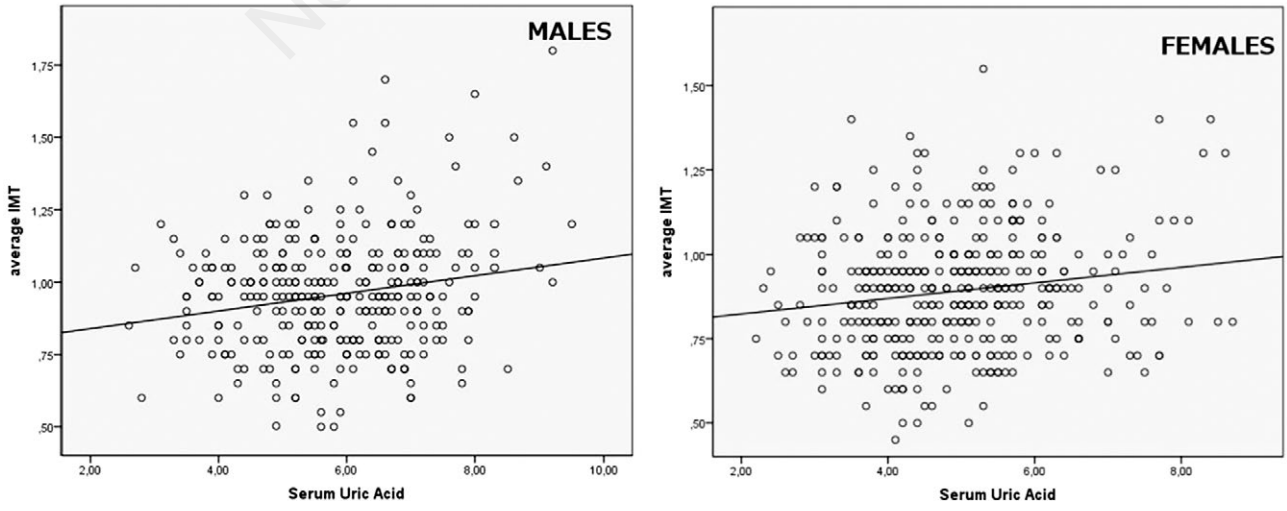

Figure 2. Relationship between serum uric acid (mg/dL) and average intimal-medial thickness (IMT) in millimetres, in males (r=0.196; p=<0.001) and females (r=0.163; p=0.001).

patients had a high CV risk, so they might not be representative for the general population. On the other hand, this could reinforce the possible further discriminating role of UA in patients with multiple CV risk factors. Furthermore, no complete data about concomitant pharmacological treatments were available in our population; thus, the possible drug influence both on IMT and carotid stiffness has not been further investigated.

Several studies have failed to demonstrate an association between UA, CV disease burden and mortality independently of other established risk factors, like hypertension [11,27-29]. Furthermore, arterial hypertension has been defined according to the values of 140/90 mmHg, despite recent studies [30]. Conversely, other researchers succeeded in this task [5,6,31-34]. In particular, Puddu *et al.* demonstrated that individuals with levels of serum UA in the higher quintiles had a higher incidence of CV disease events and higher CV and all-cause mortality [35]. A recent study showed that CV risk linearly increases with higher levels of UA, stating that it is difficult to identify a specific cut-off value that could distinguish the presence or absence of CV risk [36]. Even normal UA levels were associated with increased risk of CV events, beyond that provided by traditional risk factors [36]. This ambiguous evidence prompts the question whether UA should be considered a CV risk factor per se or just an indicator of CV risk which correlates with the presence of other established CV risk factors. Moreover, the mechanism by which UA could cause CV disease is not clear.

With the aim of identifying an intermediate end-point that could justify the exceeding CV risk in hyperuricemic patients, some authors studied the association of UA with cardiac and vascular remodelling. Iwasahima and colleagues prospectively followed 619 patients demonstrating that UA was independently associated with increased left ventricular mass, proving an exceeding rate of CV events in this population [29]. This study suggests that hyperuricemia, by means of left ventricular hypertrophy, can be an independent and powerful predictor of CV events [11]. Also, other authors have proved the association between UA and left ventricular mass in their studies [37,38]. Another group demonstrated a relationship between UA and peripheral artery disease evaluated by ankle-brachial index [39], whereas Kumral *et al.* found an independent relationship between UA and carotid artery disease in a population of patients with ischemic stroke [40].

Few groups had already explored the relationship between UA and markers of vascular damage such as carotid IMT and arterial stiffness. Viazzi and co-workers evaluated a cohort of 425 patients with essential hypertension finding a significantly higher carotid IMT and cardiac hypertrophy in hyperuricemic patients, even after adjusting for body mass index, age, creatinine clearance and high-density lipoprotein cholesterol [37]. Allopurinol treatment, which reduces the formation of UA by inhibiting the xanthine oxidase enzymatic system, was associated with lower IMT values in patients with type 2 diabetes and asymptomatic hyperuricemia [41] and lower CV events in hypertensive patients [42], but it cannot be excluded that these effects might be secondary to UA-independent effects of this drug. Other papers focused on the association between UA and Pulse Wave Velocity (PWV) showing higher values of arterial stiffness in the hyperuricemic population [38,43-47].

These findings were confirmed by a recent study that included 1680 health check participants followed for a mean period of 4.8 years showing that an increased baseline UA level is an independent risk factor and predictor for peripheral arterial stiffness as assessed by carotid-radial PWV measurements [48]. Another study found an association between UA and PWV only in men [49]. Of note, the work of Bae *et al*. reported the existence of a strict relationship between UA and arterial stiffness, but without a correlation between UA and IMT [50]. Conversely, Cicero *et al.* demonstrated a relationship between uric acid and IMT, but failed to show a relationship between UA and arterial stiffness in a multivariate

Table 2. Regression analysis assessing the capacity of UA level to predict carotid stiffness.

	Males (N=ç15)		Females (N=383)	
	Standardized Regression Coefficient	p	Standardized Regression Coefficient	p
Uric acid	*0.171*	*0.001*	*0.120*	*0.002*
Age	0.407	<0.001	0.361	<0.001
Glucose	0.018	0.727	0.028	0.469
SBP	0.112	0.085	0.494	<0.001
DBP	-0.151	0.020	-0.301	<0.001
LDL	0.010	0.848	0.188	0.851

DBP, diastolic blood pressure; LDL, low density lipoprotein cholesterol; SBP, systolic blood pressure.

Table 3. Regression analysis assessing the capacity of UA level to predict IMT stratified by gender.

	Males (N=315)		Females (N=383)	
	Standardized Regression Coefficient	p	Standardized Regression Coefficient	p
Uric acid	*0.243*	*<0.001*	*0.090*	*0.030*
Age	0.525	<0.001	0.577	<0.001
Glucose	0.006	0.899	0.046	0.272
SBP	0.128	0.029	0.027	0.633
DBP	-0.003	0.959	-0.003	0.959
LDL	0.074	0.121	0.044	0.295

SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low density lipoprotein cholesterol.

model [51]. Furthermore, UA emerged from the prospective study CARDIA [52] as an early biomarker for subclinical atherosclerosis in young adults, independent of BMI. This study demonstrated an association between UA and Coronary Artery Calcium score. A similar association was seen between UA and IMT, but only in men; stiffness was not investigated [52]. Mulè et al. demonstrated that mildly elevated UA levels were associated with higher aortic stiffness, but this association lost statistical significance after adjustment for age, blood pressure, metabolic syndrome, eGFR, and albuminuria [53]. Therefore, data in the current literature are inconclusive, leading to the statement that UA is a controversial CV risk factor.

Using high-resolution ultrasonographic techniques, in a large group of patients with high CV risk, our study highlights the independent relationship between UA and early atherosclerotic process, providing information both on IMT and local carotid arterial stiffness. This might contribute to a better comprehension of the pathophysiological mechanisms underlying the emerging evidence of the correlation between serum UA and CV morbidity and mortality.

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