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Association of Serum Uric levels and Carotid Intima Thickness with the Numbers of Organ Damaged in Hypertensive Patients

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ABSTRACT

Introduction: Target organ damage (TOD) can be evaluated in outpatient clinics and offers valuable information about patient's cardiovascular risk. Clinical evidence supported the possibility that serum uric acid (SUA) may lead to hypertension. Carotid intima–media thickness (carotid IMT) measured noninvasively by ultrasonography is now widely used as a surrogate marker for atherosclerosis. **Goal:** to investigate the association of SUA with markers of target organ damage like carotid IMT and microalbuminuria in hypertensive patients and to observe the distribution of SUA levels considering one, two, three or more TOD.

Material and methods: The study was conducted on a sample of 182 hypertensive patients. They underwent extensive clinical, laboratory, and ultrasonographic investigations searching for cardiac, vascular and renal TOD. The patients were divided into four groups as follows: no TOD (Group I, n=24); 1 TOD (Group II, n=50); 2 TOD (Group III, n=40); and ≥ 3 TOD (Group IV, n=48). Carotid IMT was performed using high-resolution B-mode ultrasonography according to Mannheim Consensus.

Results: Uric acid was directly associated with the number of affected organs. Uric acid was significantly higher in the group IV versus group III ($p<0.001$), in the group III versus group II, $p<0.001$) and in the group II versus group I ($p<0.001$). Carotid IMT was also directly associated with the number of affected organs. The value of carotid IMT was significantly higher in the group IV versus group III ($p<0.001$), in the group III versus group II, ($p<0.001$) and in the group II versus group I ($p<0.001$). We obtained a strong significantly correlation between serum uric acid levels and carotid IMT ($r=0.86$, $p<0.001$) and between carotid IMT and microalbuminuria ($r=0.74$, $p<0.001$).

Conclusion: The study showed that increased values of SUA and carotid IMT are associated with the number of TOD, thus SUA and carotid IMT may be considered indicators for evaluating TOD.

Keywords: target organ damage, essential hypertension, serum uric acid, intima-media thickness

Introduction

Cardiovascular diseases are the leading cause of death in Western countries, accounting for more than one third of all deaths. This is due mainly to the steady increase in the prevalence of hypertension and diabetes, which affect 30 and 8% of the general population, respectively, and have now reached the proportion of a worldwide epidemic.[1]

The implication of target organ damage, associated with cardiovascular disease, in the appearance of cardiovascular complications, and the possibility of adopting treatments to induce regression of such damage – with improvements in patient prognosis in some cases - make it necessary to carefully assess silent organ damage.[2]

The "target organ" effects of hypertension are particularly manifest in the heart, brain, kidney, peripheral arteries, and the eye. Indeed, hypertensive patients with evidence of target organ damage are well recognized to be at high risk of cardiovascular and cerebrovascular events, and they should be targeted for aggressive blood pressure and risk factor management [3]. Thus, the search for left ventricular hypertrophy (LVH), carotid atherosclerosis, and microalbuminuria, which likely reflect both the severity of blood pressure load and other nonhemodynamic risk factors, is currently recommended as part of global risk assessment.[4]

Uric acid, which exists almost entirely in its ionized form urate at physiological pH and is hence referred to as urate, is derived from adenine- and guanine-based purine compounds.[5] Several previous studies have suggested that serum uric acid (SUA) is an important, independent risk factor for cardiovascular (CV) disease.[6,7] Hyperuricemia predicts mortality in patients with heart failure or coronary heart disease, cerebrovascular events in individuals with diabetes, and cardiac ischemia in hypertension[8-10]. The mechanisms by which uric acid may engender organ damage is still incompletely understood, but there is increasing evidence that endothelial dysfunction is a fundamental mechanism whereby this substance may affect cardiovascular and renal function and structure.[11]

Several mechanisms have been proposed to account for the association between SUA and cardiovascular and renal abnormalities, and include: increased uric acid production to counteract oxidative stress and endothelial damage in the context of the atherosclerotic process; the severity of hypertension itself and a subtle reduction in glomerular filtration rate leading to impaired renal uric acid clearance.[12]

Study goal

The goal of the study was to investigate the association of SUA and carotid IMT with target organ damage (TOD) in hypertensive patients.

Methods

This analytical prospective study was conducted on a sample of 182 consecutive new-diagnosed patients with arterial hypertension that attended The IVth Medical Clinic of University of Medicine and Pharmacy Victor Babes Timisoara in a six month period. However, none had taken antihypertensive drugs over the 6 months before the study. The patients meeting the following criteria were excluded from the study: renal artery stenosis, coarctation of the aorta, pheochromocytoma, primary aldosteronism, Cushings's syndrome, renal disease, and increased dietary-sodium intake/drugs, or those that were taking drugs that interfere with uric acid levels and/or those with a history of gout or renal stones.

Hypertensive target organ damage was defined as the detection of one or more of the following: left ventricular hypertrophy (LVH), the presence of hypertensive retinopathy Grades 3 and 4, impaired glomerular filtration rate or microalbuminuria, or a history of a stroke, as described in agreement with European Society of Hypertension–European Society of Cardiology guidelines from 2007.[13]

The patients underwent extensive clinical, laboratory, and ultrasonographic investigations in searching for cardiac, vascular and renal TOD that comprised a medical history taken by a physician (data on age, duration of hypertension and treatment, history of cigarette smoking, current and past symptoms of cerebrovascular disease, peripheral vascular disease and coronary heart disease), anthropometric measurements, standard 12-lead ECG, carotid ultrasonic examination, and biochemical measurements.

LVH was diagnosed based on the positivity of at least one of the following ECG criteria: the voltage criteria of Cornell and of Sokolow-Lyon: Cornell voltage index ≥28 mm in men and ≥20 mm in women; Cornell product >2.440 mm ms; Sokolow-Lyon voltage index ≥35 mm; and Sokolow-Lyon product >3674 mm ms in men and >3224 in women.[14,15]

Retinal examination was carried out by an experienced ophthalmologist. Retinal changes associated with hypertension were classified into four grades using the Keith, Wagener, and Barker classification based on the level of severity of the retinal findings. Grade 1 consisted of 'mild' generalized retinal arteriolar narrowing; Grade 2 consisted of 'more severe' generalized narrowing, focal areas of arteriolar narrowing and arteriovenous nicking; Grade 3 consisted of grades 1 and 2 signs plus the presence of retinal hemorrhages, microaneurysms, hard exudates and cotton-wool spots; Grade 4 also referred to as accelerated (malignant) hypertensive retinopathy, consisted of the signs in the preceding three grades plus optic disk swelling and macular edema.[16]

Glomerular filtration rate (GFR) was estimated with CKD-EPI equation which includes serum creatinine, age, gender and race as variables, with different versions depending on ethnicity, gender and creatinine value.[17]

Stroke was identified through the history of a previous event (including transient ischemic stroke).

The patients were divided into four groups as follows:

- group I (no TOD, n=24) - without signs of organ damage
- group II (1 TOD, n=50) - with one target organ damage such as history of stroke, LVH, carotid abnormalities, retinal abnormalities or microalbuminuria
- group III (2 TOD, n=40) - with either two signs of TOD
- group IV (≥ 3 TOD, n=48) - with 3 or more signs of TOD

Anthropometric measurements

Height and weight were measured without shoes and wearing light clothing by a trained nurse. Height was rounded to the nearest 1 cm, and weight to the nearest 100 g. Body mass index (BMI) was calculated using the formula: BMI = weight (in kilograms)/height (in meters) squared.

Hypertension was defined in the presence of antihypertensive medications or according to standard criteria, such as clinic systolic BP ≥ 140 mm Hg and/or diastolic BP ≥ 90 mm Hg on at least two different occasions prior to the study day.

Blood pressure was measured using an automated sphygmomanometer with the subject in a sitting position. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured at the first and fifth Korotkoff phases, respectively. Three consecutive readings were performed and the average was recorded. None of the hypertensive patients were on medication at the time of the study.

Laboratory procedure

The blood samples were collected from the antecubital vein between 8 a.m. and 10 a.m., in a sitting position, after a 12 h of fasting and avoiding alcohol.

The biochemical values included total cholesterol, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting plasma glucose, serum creatinine and serum uric acid. Concentrations of TC, HDL-C, TG and serum creatinine levels were measured with enzymatic methods on an automated clinical chemistry analyzer (Dimension RxL Max, Siemens Healthcare Diagnostics) using original reagents from Siemens Healthcare Diagnostics. The LDL-cholesterol concentration was calculated using Friedewalds' equation.[18]

Serum creatinine and uric acid levels were measured in the routine laboratory by an automated technique based on the measurement of Jaffe chromogen and by the URICASE/POD (Boehringer Mannheim, Mannheim, Germany) method implemented in an autoanalyzer. Hyperuricemia was defined as serum uric acid > 7 mg/dL in men and > 6.5 mg/dL in women.

Microalbumin was measured after a 24-hour urine collection using a nephelometric immunoassay (normal range, 0–29 mg per 24 h). Microalbuminuria was defined as urinary albumin excretion ranging between 30 and 299 mg per 24 h.[19]

Carotid ultrasonography

Carotid IMT was performed using high-resolution B-mode ultrasonography according to Mannheim Consensus.[20] Both carotid arteries were monitored in terms of carotid intima-media thickness (carotid IMT) in all patients using the high-resolution ultrasound system equipped with a mechanical sector probe with a 7.5 MHz annular imaging transducer. Patients were laid in supine position with mild hyperextension of the neck to allow optimal visualization of the common carotid artery. The mid and distal portions of the common carotid artery, carotid bulb, and the proximal portions of the internal and external carotid arteries were systematically examined manually in short-axis and long-axis views. We measured the thickness of the intima-media on the far wall of the bilateral common carotid artery about 10-mm proximal to the bifurcation of the carotid arteries on the B-mode monitor and used the mean values for the study. Carotid plaque was defined as IMT ≥ 1.3 mm. Each measurement was calculated by taking the average of 3 readings. Carotid abnormalities were diagnosed when there was ≥ 1 carotid plaque or when there was diffuse common carotid artery thickening defined as an average IMT ≥0.9 mm.

The study protocol was approved by the Ethics Committee of the Clinic and all patients provided written informed consent prior to their participation.

Statistical analysis

The Student's t-test was used for comparisons of continuous data, while the chi(2) test was used for comparisons of categorical variables. $P < 0.05$ (2-tailed test) was considered statistically significant. The Bravais-Pearson coefficient was used to correlate data.

Results

The baseline characteristics of study subjects according to target organ damage distribution are presented in table 1.

Uric acid was higher in the patient groups with > or=3 TOD (Group IV: 8.38±0.31mg/dl vs Group III: 8.24 ±0.42 mg/dl, P<0.001), 2 TOD (Group III: 8.24±0.42 mg/dl vs Group II: 7.91±0.76 mg/dl, P<0.001) and 1 TOD as compared with patients with no TOD (Group II: 7.91±0.76 mg/dl vs Group I: 6.04 ± 0.41, P<0.001) (Figure 1).

Carotid IMT was also directly associated with the number of affected organs. The value of carotid IMT was higher in the patient groups with > or=3 TOD (Group IV: 1.30±0.04 mm vs Group III: 1.29±0.04 mm, p<0.001), 2 TOD (Group III: 1.29±0.04 mm vs Group II: 1.22±0.11 mm, p<0.001) and 1 TOD as compared with patients with no TOD (Group II: 1.22±0.11 mm vs Group I: 0.84±0.3 mm, p<0.001).

A positive correlation was found between serum uric acid concentration and intima-media thickness (r = 0.86, p < 0.001) (Figure 3), and between serum uric acid and microalbuminuria (r = 0.64, p < 0.001) (Figure 4).

Discussion

The association between SUA and early hypertensive and atherosclerotic organ damage is intriguing and suggests that mild hyperuricemia might be a marker of incipient cardiovascular involvement.[12] Currently hypertension grips around 25% of the entire world population and epidemiologic studies have found that hyperuricemia is an independent risk factor for renal dysfunction in a general population, in hypertensive patients and in stroke patients.[21-24]

Other studies proved that high UA levels that have been associated with organ damage in hypertensive patients are considered an integral part of the biochemical alterations that compound the metabolic syndrome. Indeed, in these studies, serum UA was higher in hypertensive patients with target organ damage, as well as in seemingly healthy men.[12,25]

Several studies have shown the association between hyperuricemia and microalbuminuria in hypertensive patients.[12,26] Until now, it is unknown whether increased uric acid level and high blood pressure have synergistic effects on microalbuminuria.[27] Uric acid–mediated arteriolopathy and interstitial inflammation suggest mechanisms that would exacerbate or potentiate progressive renal functional decline after injury, also known as renal progression.[28]

In the study done in the Turkish population by Tavil and collaborators, it was found that IMT was increased in patients with hypertension independently of hyperuricemia when compared with control subjects. However, subjects presenting both hypertension and hyperuricemia had increased carotid IMT compared to those with normal uric acid levels. In addition, there were significant associations between carotid IMT measurement, serum uric acid level, and other major atherosclerotic risk factors.[29,30]

A possible associations between uric acid and carotid atherosclerosis have been most intensively analyzed in the Atherosclerosis Risk in Communities (ARIC) Study, which included >10 000 subjects. In that study, Iribarren and collaborators showed that the association between uric acid and carotid atherosclerosis, assessed by the average intima-media thickness, was statistically significant in white men but not women after adjusting for age, BMI, waist-to-hip ratio,

systolic blood pressure, fibrinogen, low-density lipoprotein cholesterol, HDL-C, and ARIC center.[31]

Similar with the results of these studies, in our study, SUA levels were positive and significantly correlated with carotid atherosclerosis (measured by carotid ultrasonography), and microalbuminuria (an established marker of kidney damage in hypertensive patients according to the guidelines of the European Society of Hypertension and of JNC-7)[17], in a group of untreated arterial hypertension patients. The present study showed also that both SUA levels and carotid IMT values were in relation with the number of organ damaged in a linear dependent manner.

Prospective randomized studies targeting uric acid reduction with allopurinol or uricosuric agents are necessary to finish the controversy of the atherogenity of uric acid. At any rate concomitant risk factors like abdominal obesity, dyslipidemia and hypertension must be aggressively treated with changes in life-style and pharmacological therapy if necessary.[32]

The present study has some limitations. The correlation of serum uric acid with other parameters like carotid IMT or microalbuminuria was done in a non-selected population of hypertensive patients. Therefore, the study comprised patients independently of the duration or the severity of arterial hypertension. This possibly affects both myocardial and kidney performance. Another limitation of the study was that our exclusion criteria limitated the number of subjects enrolled. Because our study comprised a relatively small patient population we consider that our results should be tested in a larger scale study.

Conflict of Interest: none

Conclusion

The study showed that increased values of SUA and carotid IMT are associated with the number of TOD, thus serum uric acid and carotid IMT may be considered valuable indicators for evaluating TOD in hypertensive patients.

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Table 1: Baseline characteristics of study subjects according to target organ damage distribution.

PARAMETERS	Group I No TOD (n=24)	Group II 1 TOD (n=50)	Group III 2 TOD (n=40)	Group IV ≥ 3 TOD (n=48)
Age (years)	54 ± 4.80	58 ± 4.94	58 ± 4.73	59 ± 4.73
Sex M/F (%)	33/67	38/62	37/63	39/61
Smokers (%)	20	30	30	41
BMI (kg/m^2)	25	30	40	45,8
SBP (mmHg)	148 ± 5.07	166 ± 10.91	171 ± 8.73	175 ± 6.58
DBP (mmHg)	88 ± 2.52	92 ± 4.74	93 ± 6.17	94 ± 3.99
TC (mg/dL)	181 ± 7.15	205 ± 24.35	208 ± 22.28	209 ±19.17
TG (mg/dL)	138 ±10.38	164 ± 17.19	164 ± 17.99	169 ± 13.18
LDL –C (mg/dL)	107 ± 6.68	130 ± 24.88	134 ± 23.26	135 ± 19.63
HDL - C (mg/dL)	47 ± 4.30	42 ± 6.16	41 ± 6.30	40 ± 5.02
Fasting plasma glucose (mg/dL)	78 ± 6.21	111±26.36	118 ± 31.43	126± 37.15
Serum creatinine (mg/dL)	0.81 ± 0.13	0.95±0.13	0.97 ± 0.13	0.97 ± 0.11
Estimated GFR (ml/min/1,73 m^2)	94 ± 2.04	76±6.59	75 ± 4.94	71 ± 1.44
Microalbuminuria (mg/L)	13 ± 5.93	93±32.20	97 ± 24.41	111 ± 20.70
SUA levels (mg/dL)	6.04 ± 0.41	7.91±0.76	8.24 ± 0.42	8.38 ± 0.31
Carotid IMT (mm)	0.84 ± 0.03	1.22±0.11	1.29 ± 0.04	1.30 ± 0.04

BMI indicates body mass index; TC, total cholesterol; TG, triglycerides; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; Estimated GFR, estimated glomerular filtration rate; SUA levels, serum uric acid levels; Carotid IMT, Carotid intima-media thickness;

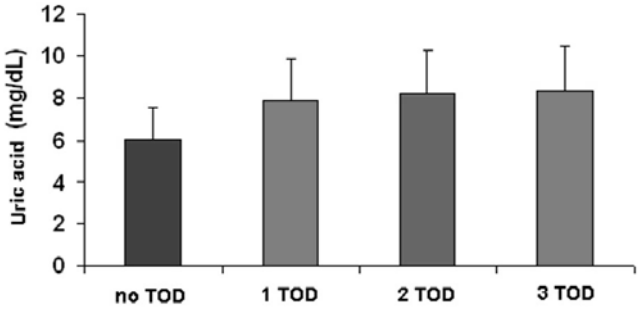

Figure 1: Distribution of SUA levels considering the number of target organ damage

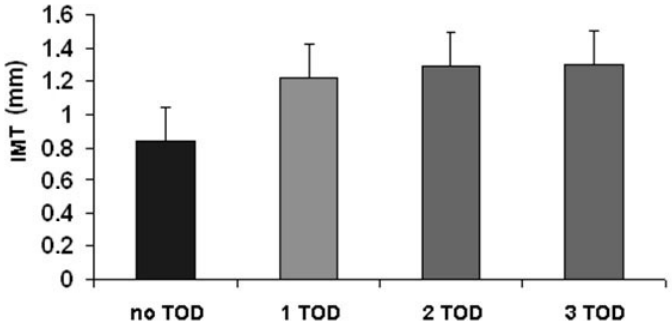

Figure 2: Distribution of IMT values considering the number of target organ damage

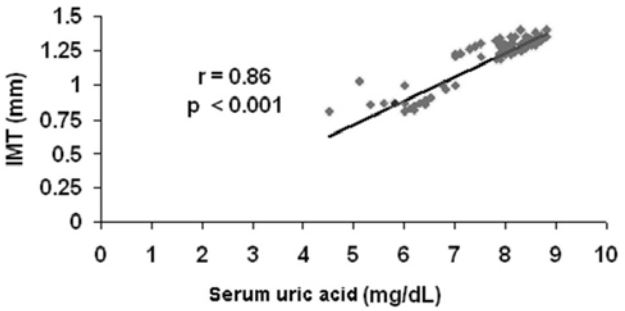

Figure 3: Correlation between carotid IMT and serum uric acid

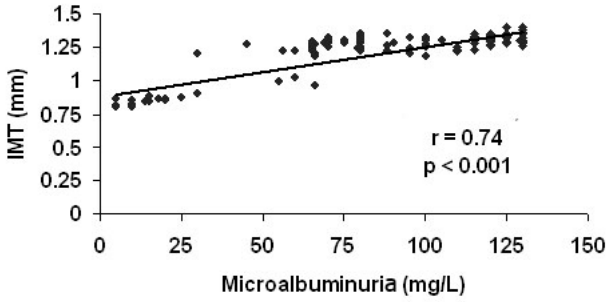

Figure 4: Correlation between carotid IMT and microalbuminuria