

## THE ROLE OF HYPERURICEMIA IN ENDOTHELIAL DYSFUNCTION INDUCED BY HYPERTENSION

GERMAINE SĂVOIU\*, CORINA ȘERBAN\*, LAVINIA NOVEANU\*\*, O. FIRĂ-MLADINESCU\*,  
D. GAIȚĂ\*\*\*, OANA M. DUICU\*, ANCA TUDOR\*\*\*\*, DANINA MUNTEAN\*,  
GEORGETA MIHALAȘ\*\*

\* Department of Pathophysiology, "Victor Babeș" University of Medicine and Pharmaceutics,  
Timișoara

\*\* Department of Physiology, "Victor Babeș" University of Medicine and Pharmaceutics, Timișoara

\*\*\* Department of Preventive Cardiology and Rehabilitation, "Victor Babeș" University of Medicine  
and Pharmaceutics, Timișoara

\*\*\*\* Department of Medical Informatics, "Victor Babeș" University of Medicine and Pharmaceutics,  
Timișoara

*Abstract.* Hyperuricemia (HU) is a well recognized risk factor for cardiovascular diseases. Intima-media thickness (IMT) of the carotid artery noninvasively assessed by ultrasonography is now validated as a sensitive marker for atherosclerosis and it is directly associated with increased risk of cardiovascular disease. The aim of this study was to evaluate the correlations between IMT and uric acid levels in patients with hypertension (HT). Our study consisted of a group of 30 patients with HT without HU (male 58%, mean age  $\pm$  S.D.:  $49 \pm 10$  years), a group of 25 patients with HT and HU (male 52%, mean age  $\pm$  S.D:  $52 \pm 10$  years), and a control group of 25 healthy subjects (male 55%, mean age  $\pm$  S.D:  $50 \pm 11$  years). All patients in the study groups were examined by high resolution B-mode ultrasound to measure the IMT of the common carotid artery. IMT values were significantly higher in the hypertensive patients groups with and without HU, compared to the control group ( $0.98 \pm 0.28$  mm,  $1.41 \pm 0.31$  mm *versus*  $0.56 \pm 0.15$  mm, respectively,  $p < 0.001$ ). All patients with HU had significantly higher carotid IMT compared to the patients without HU. In this study we have shown that higher serum uric acid levels are associated with atherogenesis independent from hypertension.

*Key words:* Hyperuricemia, IMT, atherosclerosis, cardiovascular risk factors.

### INTRODUCTION

More than 50 years ago, Gertler noted an association between elevated levels of serum UA and coronary heart disease [9]. Since then, several studies have attempted to establish whether UA is related to CHD events, independent of the known CHD risk factors [4, 8, 13, 20]. The relationship between hyperuricemia and other cardiovascular risk factors such as, hypertension, obesity, physical effort

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and HDL-cholesterol diminution, have been demonstrated in many clinical studies, but the pathogenic mechanisms have not been clarified yet [18]. Several proatherogenic properties have been attributed to UA including activation of endothelial cells, platelet activation, and increased platelet adhesiveness. UA has also been implicated in the pathogenesis of hypertension [10].

The thickness of the common carotid intima-media (IMT) measured by a noninvasive ultrasound technique is used as a marker of atherosclerotic disease and is directly associated with a high cardiovascular risk factor [5, 7].

Some other studies have reported that a high IMT value is strongly correlated with an increase of cardiovascular morbidity in patients with hypertension and hyperuricemia, but the role of hyperuricemia in the atherosclerosis process has been not elucidated yet.

The principal goal of this study was to measure carotid intima-media thickness in hypertensive patients, with or without hyperuricemia.

## MATERIALS AND METHODS

The study included 3 groups: the first group consisted of 30 patients (male 58%, mean age  $\pm$  standard deviation:  $49 \pm 10$ ) with hypertension (HT) without hyperuricemia (HU); the second group consisted of 25 patients with HT and HU (male 52%, mean age  $\pm$  standard deviation:  $52 \pm 10$ ); and the third group, was the control group represented by 25 healthy subjects (male 55%, mean age  $\pm$  standard deviation:  $50 \pm 11$ ). The subjects from the control group had no cardiovascular or other systemic diseases and physical examination, electrocardiogram, chest radiography and two-dimensional Doppler echocardiography were normal.

Hypertension was defined as a systolic BP of  $>140$  mmHg and/or a diastolic BP of  $>90$  mmHg as mean of three measurements in at least three visits at 1-week intervals or receiving antihypertensive treatment [21].

Hyperuricemia was defined as the serum levels of  $> 410$   $\mu\text{mol/L}$  in men, and  $>310$   $\mu\text{mol/L}$  in women [14].

Total cholesterol, HDL cholesterol, LDL cholesterol and triglyceride levels were measured using standard enzymatic methods (Boehringer-Mannheim) with a fully automated analyzer (model 717 Roche/Hitachi; Tokyo, Japan). SUA levels were determined with an enzymatic colorimetric method.

Exclusion criteria were systolic blood pressure of 220 mmHg or higher, ischemic heart disease, acute coronary syndrome, stroke, or presence of a major illness such as cancer, liver disease, renal insufficiency, insulin-treated diabetes and depression.

## CAROTID ULTRASONOGRAPHY

Subjects were investigated with a high-resolution B-mode operation system with linear transducers with 17 MHz frequency. To obtain a quality image, the

optimal focal distance was between 30–40 mm, the optimum frames frequency 25 Hz and we have done amplification setups (for minimal intraluminal artifacts). The compensatory amplification was about 60 dB. Each subject rested in the supine position for several minutes in a temperature-controlled room. The brachial artery was identified at 5 cm proximal to the transient bifurcation by using this High-resolution B-mode ultrasonography. After baseline imaging, a right arm cuff was inflated to > 50 mm Hg above systolic blood pressure, for 5 minutes. After the cuff was deflated ischemia-induced distal hyperemia produced a transient increase of artery diameter. The relative change in mean arterial diameter was calculated as: % Dilation = [Maximum diameter-Baseline diameter] × 100 / Baseline diameter, where maximum diameter was the maximum mean diameter observed at 45–60 seconds after cuff release.

For carotid ultrasound study, the image was focused on the posterior (far) of the left carotid artery. A minimum of 4 measurements of the common carotid far wall were taken 10 mm proximal to the bifurcation to derive mean carotid IMT.

#### STATISTICAL ANALYSIS

All the numerical variables were expressed as mean ± SD (standard deviation). Means were compared using analysis of variance of the Student t-test and Pearson's correlation was used to test correlations and results. Statistical significance was defined as two-sided  $p < 0.05$ . The Anova One Way and Post Hoc Bonferroni tests were used to compare data. All statistical analyses were performed using *Excel Microsoft Office 2003*.

#### RESULTS

Demographic data, distribution of traditional CV risk factors and the laboratory patient's data are shown in Table 1. There is no significant statistical difference between groups concerning sex, age, cardiovascular profile risk and medical cardiovascular therapy, except for the serum total cholesterol (TC), triglycerides (TG) and low density lipoprotein-cholesterol (LDL-C) (Table 1).

The correlation between serum uric acid level and IMT in the control group was direct, strong and significant ( $\alpha = 0.01$ ) (Fig. 1).

Table 1

Physical characteristics and biochemical parameters of the study subjects

	Control group (n = 25)	Group with HT without HU (n = 30)	Group with HT and HU (n = 25)
Age (years)	50 ± 11	49 ± 10	52 ± 10
Male (%)	55	58	52

Table 1 (continued)

Total cholesterol (mg/dL)	175 ± 20	223 ± 22	236 ± 41
LDL-cholesterol (mg/dL)	125 ± 21	135 ± 22	166 ± 38
HDL-cholesterol (mg/dL)	47 ± 10	42 ± 11	33 ± 7
Triglycerides (mg/dL)	112 ± 15	154 ± 21	180 ± 72
Systolic blood pressure (mm Hg)	115 ± 20	150 ± 23	183 ± 19
Diastolic blood pressure (mm Hg)	75 ± 9	110 ± 20	98 ± 5
Plasma creatinine (mg/dL)	0.83 ± 20	0.97 ± 20	1.02 ± 21
Uric acid (μmol/L)	277 ± 110	272 ± 52	473 ± 38
Carotid IMT (mm)	0.56 ± 0.15	0.98 ± 0.28	1.41 ± 0.31

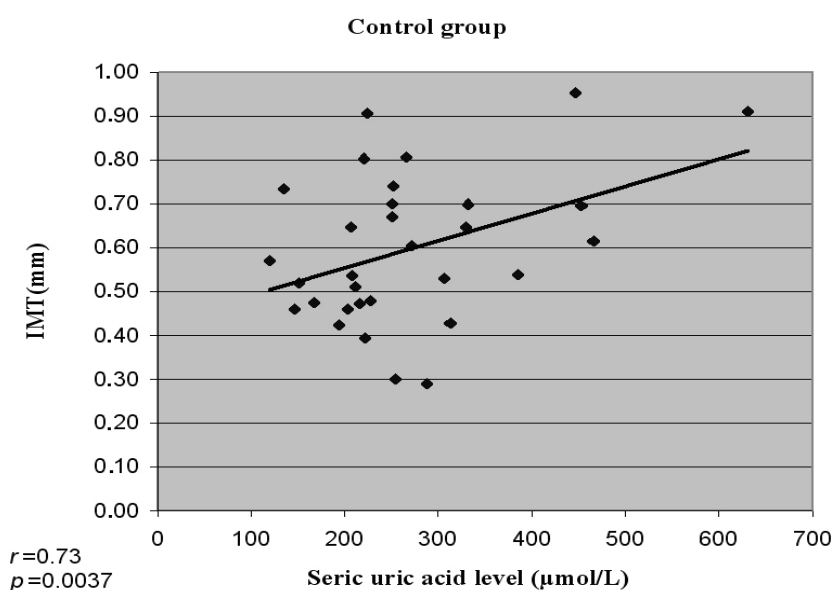


Fig. 1. The correlation between serum uric acid level and IMT in the control group.

In the group with HT without HU we found a direct, medium and significant correlation between serum uric acid level and IMT ( $\alpha = 0.05$ ) (Fig. 2) and in the group with HT and HU, the correlation between serum uric acid level and IMT was direct, strong and significant ( $\alpha = 0,001$ ) (Fig. 3).

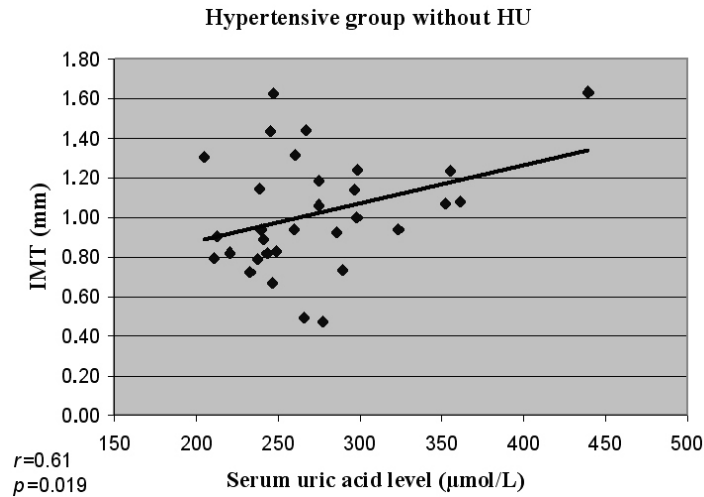


Fig. 2. The correlation between serum uric acid level and IMT in the group with HT without HU.

We also noticed that IMT values were significantly higher in patients with hypertension as compared with the control group. In the other two groups, with arterial hypertension, the patients with HU presented elevated IMT values comparatively with the patients without HU.

It was obtained the value of  $p < 0.001$ , meaning that between the IMT values for the three groups, the differences were significant ( $\alpha = 0.001$ ).

The values were compared for two by two groups, and in each case  $p$  was  $< 0.001$ , meaning that there were significant differences ( $\alpha = 0.001$ ).

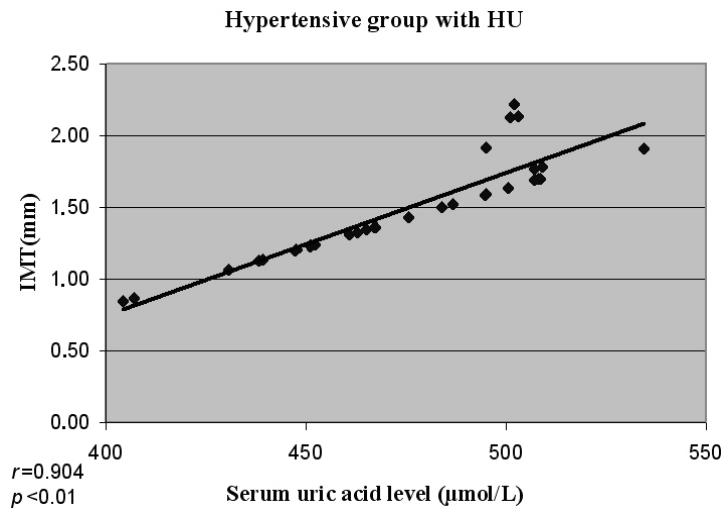


Fig. 3. The correlation between serum uric acid level and IMT in the group with HT and HU.

## DISCUSSIONS

Presently, hyperuricemia is often considered as a part of metabolic syndrome or just a marker of other coronary risk factors such as hypertension, dyslipidemia, obesity or renal disease [11]. Many studies point out that a high serum uric acid level may be an independent risk factor associated with cardiovascular events [1, 2, 21].

Uric acid has been shown to stimulate production of monocyte chemoattractant protein-1 (MCP-1) by vascular smooth muscle cells, interleukin-1, interleukin-6, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) by human mononuclear cells, and CRP by cultured human vascular cells. Infusion of UA into mice leads to a marked increase in circulating TNF- $\alpha$  level [6, 11]. On the other hand, because serum urate has free radical scavenging and antioxidant properties, it has been suggested that elevation of UA levels occurs in response to systemic inflammation [12]. Exogenous uric acid gives rise to endothelial dysfunction, and endogenous uric acid concentrations correlate with the extent of endothelial dysfunction [3, 19].

Recent studies have shown that early diagnosis of atherosclerosis is an important step in prevention of cardiovascular diseases [3]. Anterior reports suggested that IMT is the most studied and useful sonographic marker for precocious atherosclerosis and IMT measure was also postulated as a surrogate marker for generalized atherosclerosis [5].

Even though hyperuricemia is often seen in hypertensive patients, the connection between them and the pathogenic mechanism is still unclear. The present study was made in order to observe if hyperuricemia has a possible role in developing atherosclerosis in patients with hypertension.

In our study we showed that IMT is higher in patients with hypertension, with or without hyperuricemia, comparatively with the control group. We proved that this difference also exists between the two groups of hypertensive patients. We noticed that there were significant correlations between IMT, serum uric acid levels and other cardiovascular risk factors. These results indicate that high levels of serum uric acid are associated with the atherogenic process, independently of hypertension.

Therefore, high levels of uric acid may be associated with atherosclerosis development and the action is independent among the other atherosclerotic risk factors. The uric acid also influences the negative effects of hypertension on the cardiovascular system in hypertensive patients.

## CONCLUSION

In this study we noticed that carotid IMT is increased in patients with hypertension, with or without hyperuricemia, comparatively to the control group patients (without hypertension). In hypertensive patients with hyperuricemia IMT

was higher than in hypertensive patients without hyperuricemia. These results suggest that higher serum uric acid levels are associated with atherogenesis. Therefore, early screening for hyperuricemia and lowering serum uric acid levels might be beneficial in slowing progression of IMT in hypertensive patients.

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