THE ROLE OF URIC ACID AS A RISK FACTOR FOR ARTERIAL HYPERTENSION

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Summary

Hyperuricemia (HU) is associated with hypertension, vascular disease, and renal disease and is a well recognized risk factor for cardiovascular diseases. Carotid Intima-media thickness (IMT) of the carotid arteries assessed noninvasively by ultrasonography is now validated as a sensitive marker for atherosclerosis and it is directly associated with increased risk of cardiovascular disease and is predictive of future cardiovascular events. The aim of this study was to evaluate the role of uric acid as a risk factor for cardiovascular disease and arterial hypertension (HTA). Our study consisted of a group of 85 patients with HTA without HU (male 58%, mean age ± S.D.: 49 ± 10 years), a group of 80 patients with HTA and HU (male 52%, mean age ± S.D: 52 ± 10 years), and a control group of 80 healthy subjects (male 55%, mean age ± S.D: 50 ± 11 years) hospitalized in the IV Medical Clinic of University of Medicine and Pharmacy “Victor Babes” Timisoara in a one year period. The patients underwent complete clinical and paraclinical investigations (systolic and diastolic blood pressure, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides and serum uric acid). All the patients in the study groups were also 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 ± 0.28 mm, 1.41 ± 0.31 mm versus 0.56 ± 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 independently from hypertension. Early screening for hyperuricemia and lowering serum uric acid levels might be beneficial in slowing progression of IMT in hypertensive patients.

Key words: uric acid, HTA, IMT savoiugema@yahoo.com

Introduction

The relationship between hyperuricemia and other cardiovascular risk factors such as, hypertension, obesity, physical effort and HDL-cholesterol diminution, have been demonstrated in many clinical studies, but the pathogenic mechanisms have not been yet clarified (Ward, 1998).

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-α (TNF-α) by human mononuclear cells, and CRP by cultured human vascular cells. Infusion of uric acid into mice leads to a marked increase in circulating TNF-α level (Kanellis, 2003). On the other hand, because serum urate has free radical scavenging and antioxidant properties, it has been suggested that elevation of uric acid levels occurs in response to systemic inflammation (Kanellis, 2005).
Exogenous uric acid gives rise to endothelial dysfunction, and endogenous uric acid concentrations correlate with the extent of endothelial dysfunction (Waring, 2000). Several proatherogenic properties have been attributed to uric acid including activation of endothelial cells, platelet activation, and increased platelet adhesiveness. Uric acid has also been implicated in the pathogenesis of hypertension (Johnson, 2003).

The present study was designed in order to observe if hyperuricemia has possible role in developing atherosclerosis in patients with arterial hypertension.

**Material and methods**

The study included 3 groups: the first group consisted of 85 patients (male 58%, mean age ± standard deviation: 49±10) with hypertension (HT) without hyperuricemia (HU); the second group consisted of 80 patients with HT and HU (male 52%, mean age ± standard deviation: 52±10); and the third group, was the control group represented by 80 healthy subjects (male 55%, mean age ± standard deviation: 50±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 (WHO guidelines, 1999).

Hyperuricemia was defined as the serum levels of > 410 µmol/l in men, and >310 µmol/l in women (Ruilope, 2001).

**Carotidian 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 has to be between 30-40 mm, the optimal frame’s frequency 25 Hz and amplification setups must be done (for minimal intraluminal artifacts). The compensatory amplification has to be 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 transiently 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 (SBP), 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] x 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 numeric 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 I.
TABLE I
Physical characteristics and biochemical parameters of the study subjects

<table>
<thead>
<tr>
<th></th>
<th>Control group (n=80)</th>
<th>Group with HT without HU (n=80)</th>
<th>Group with HT and HU (n=85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50 ± 11</td>
<td>49 ± 10</td>
<td>52 ± 10</td>
</tr>
<tr>
<td>Male (%)</td>
<td>55</td>
<td>58</td>
<td>52</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>175 ± 20</td>
<td>223 ± 22</td>
<td>236 ± 41</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dL)</td>
<td>125 ± 21</td>
<td>135 ± 22</td>
<td>166 ± 38</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>47 ± 10</td>
<td>42 ± 11</td>
<td>33 ± 7</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>112 ± 15</td>
<td>154 ± 21</td>
<td>180 ± 72</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>115 ± 20</td>
<td>150 ± 23</td>
<td>183 ± 19</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>75 ± 9</td>
<td>110 ± 20</td>
<td>98 ± 5</td>
</tr>
<tr>
<td>Plasma creatinine (mg/dL)</td>
<td>0.83 ± 20</td>
<td>0.97 ± 20</td>
<td>1.02 ± 21</td>
</tr>
<tr>
<td>Uric acid (µmol/L)</td>
<td>277 ± 110</td>
<td>272 ± 52</td>
<td>473 ± 38</td>
</tr>
<tr>
<td>Carotid IMT (mm)</td>
<td>0.56 ± 0.15</td>
<td>0.98 ± 0.28</td>
<td>1.41 ± 0.31</td>
</tr>
</tbody>
</table>

There is no significant statistical difference between groups concerning sex, age, cardiovascular profile risk and medical cardiovascular therapy, except of the serum total cholesterol (TC), triglycerides (TG) and low density lipoprotein – cholesterol (LDL – C). The correlation between serum uric acid level and IMT in the control group was direct, strong and significant (α = 0.01) (fig.1).

**Figure 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 (α = 0.05) (figure 2) and in the group with HT and HU, correlation between serum uric acid level and IMT was direct, strong and significant (α = 0.001) (figure 3).

We also noticed that IMT values were significant higher in patients with hypertension, comparative 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 (α=0.001).

**Figure 2- The correlation between serum uric acid level and IMT in the group with HT without HU**

**Figure 3- The correlation between serum uric acid level and IMT in the group with HT and HU**
The values were compared for two by two groups, and in each case p was <0.001, meaning that there were significant differences (α=0.001).

Discussion

More than 50 years ago, Gertler noted an association between elevated levels of serum UA and coronary heart disease (Gerter, 1951). Since then, several studies have attempted to establish whether UA is related to CHD events, independent of the known CHD risk factors (Fanget al., 2000, Wheeler et al., 2005).

Elevated levels of serum uric acid may be due to increased dietary intake of purines, increase in uric acid production, or decrease in its excretion. Differences in alcohol consumption, exercise, or dietary purine intake may cause transient hyperuricemia (Maclachlan, 1967).

Essential hypertension is consistently associated with endothelial dysfunction (Panza, 1990) and hyperuricemia is a strong predictor of hypertension and blood pressure progression (Sundstrom, 2005). Therefore, individuals with essential hypertension constitute an interesting population in which to investigate the relationship between uric acid and endothelial dysfunction.

Even though hyperuricemia is often seen in hypertensive patients, the connection between them and the pathogenic mechanism is still unclear. Hyperuricemia has been linked to cardiovascular and renal diseases, possibly through the generation of reactive oxygen species (ROS) and subsequent endothelial dysfunction. 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 is not yet elucidated.

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 directed associated with a high cardiovascular risk fact (Davis, 2001).

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.

Conclusion

Early screening for hyperuricemia and lowering serum uric acid levels might be beneficial in slowing progression of IMT in hypertensive patients. Thus, hyperuricemia induces endothelial dysfunction; this may provide insight into a pathogenic mechanism by which uric acid may induce hypertension and vascular disease.

References


Kanellis, J., Watanabe, S., Li, J.H., et al. Uric acid stimulates monocyte chemoattractant