Serum Uric Acid and Target Organ Damage in Primary Hypertension

Francesca Viazzi, Denise Parodi, Giovanna Leoncini, Angelica Parodi, Valeria Falqui, Elena Ratto, Simone Vettoretti, Gian Paolo Bezante, Massimo Del Sette, Giacomo Deferrari, Roberto Pontremoli

Abstract—The role of serum uric acid as an independent risk factor for cardiovascular and renal morbidity is controversial. A better understanding of its relationship with preclinical organ damage may help clarify the mechanism(s) implicated in the development of early cardiovascular disease. We evaluated the association between uric acid and the presence and degree of target organ damage in 425 (265 males, 160 females) middle-aged, untreated patients with essential hypertension. Left ventricular mass index and carotid intima-media thickness were assessed by ultrasound scan. Albuminuria was measured as the albumin to creatinine ratio in 3 nonconsecutive first morning urine samples. Overall, patients with target organ damage had significantly higher levels of serum uric acid as compared with those without it (presence versus absence of left ventricular hypertrophy, \( P = 0.04 \); carotid abnormalities, \( P < 0.05 \); microalbuminuria, \( P < 0.004 \); and at least 1 versus no organ damage, \( P < 0.03 \)). In women, the occurrence and severity of each target organ damage we examined increased progressively from the lower to the upper serum uric acid tertiles (\( P < 0.01 \)). After adjustment for body mass index, age, creatinine clearance, and high-density lipoprotein cholesterol, each standard deviation increase in serum uric acid entailed a 75% higher risk of having cardiac hypertrophy and a 2-times greater risk of having carotid abnormalities. These results support the role of serum uric acid as an independent, modifiable marker of cardiovascular damage. (Hypertension. 2005;45:991-996.)

Key Words: atherosclerosis ■ gender ■ hypertension ■ risk factors ■ uric acid

A number of studies have shown that serum uric acid (SUA) plays a role in the development of cardiovascular morbidity in the general population,1–4 as well as in patients with hypertension,5–7 type II diabetes,8 and cardiac or vascular diseases.9–12 A meta-analysis of data taken from 8 trials that were performed on hypertensive patients showed that each standard deviation (SD) increment in SUA entails an augmentation of cardiovascular risk that equals what is observed for similar changes in blood pressure or total cholesterol.13 However, the independent role of SUA as a risk factor has been undergoing debate for years. In fact, mild hyperuricemia is often a concomitant finding of obesity, lipid abnormalities, and insulin resistance, all of which are components of the metabolic syndrome (MS). Accordingly, in some studies on white as well as Asian populations, the direct relationship that is observed between uric acid and cardiovascular mortality weakens or disappears after adjusting for confounding factors.14–16

Several pathophysiological mechanisms linking SUA to cardiovascular damage at the cellular and tissue level have been proposed, including proliferation of vascular smooth muscle cells,17 stimulation of the inflammatory pathway,18 and possible prothrombotic effects mediated by platelet activation.19 In addition, uric acid has proved to be an excellent marker for tissue ischemia and endothelial dysfunction,11,20 and it has been shown to play a role in the development of atherosclerotic lesions.21

The presence of subclinical hypertensive organ damage signals a condition of increased risk for cardiovascular and renal morbidity and mortality. 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.22 Because the role of SUA in the development of cardiovascular disease is receiving growing attention, a better understanding of its relationship with subclinical hypertensive target organ damage (TOD) may help clarify the pathophysiological mechanism(s) underlying this association. The present study was therefore performed to evaluate the association between SUA levels and the presence and degree of preclinical organ damage in a group of middle-aged, untreated patients with essential hypertension.

Patients and Methods

Between January 1998 and July 2002, all patients with primary hypertension attending the outpatient clinic of our institution were asked to participate in this study, which was part of a larger trial.
Table 1. Descriptive Characteristics of Study Patients on the Basis of Serum Uric Acid Levels and Gender

<table>
<thead>
<tr>
<th>Variable</th>
<th>All</th>
<th>SUA tertiles</th>
<th>P</th>
<th>SUA tertiles</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>I</td>
<td>II</td>
<td>III</td>
<td>I</td>
</tr>
<tr>
<td>No.</td>
<td>425</td>
<td>425</td>
<td>425</td>
<td>425</td>
<td>425</td>
</tr>
<tr>
<td>Age, years</td>
<td>47±9</td>
<td>48±10</td>
<td>47±11</td>
<td>48±8</td>
<td>NS</td>
</tr>
<tr>
<td>BMI 26.4±3.6</td>
<td>26.3</td>
<td>26.3</td>
<td>28.3*</td>
<td>28.4*</td>
<td>0.0003</td>
</tr>
<tr>
<td>Reported duration of hypertension, mos</td>
<td>52±57</td>
<td>50±49</td>
<td>51±63</td>
<td>56±53</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>157±17</td>
<td>156±17</td>
<td>154±21</td>
<td>157±16</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>101±8</td>
<td>101±8</td>
<td>102±7</td>
<td>102±8</td>
<td>NS</td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td>119±12</td>
<td>119±9</td>
<td>118±17</td>
<td>118±17</td>
<td>NS</td>
</tr>
<tr>
<td>Serum uric acid, μmol/L</td>
<td>306±84</td>
<td>282±42</td>
<td>354±16</td>
<td>420±36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum glucose, mmol/L</td>
<td>5.0±0.6</td>
<td>5.1±0.6</td>
<td>5.0±0.7</td>
<td>5.2±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine, mmol/L</td>
<td>80±18</td>
<td>89±18</td>
<td>89±18</td>
<td>89±18</td>
<td>NS</td>
</tr>
<tr>
<td>Estimated creatinine clearance, ml/min</td>
<td>87±21</td>
<td>91±21</td>
<td>93±21</td>
<td>88±18</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.4±0.7</td>
<td>1.3±0.6</td>
<td>1.5±0.6</td>
<td>1.8±1.0*</td>
<td>0.001</td>
</tr>
<tr>
<td>Total serum Cholesterol, mmol/L</td>
<td>5.46±1.11</td>
<td>5.41±1.11</td>
<td>5.54±1.16</td>
<td>5.57±1.24</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-Cholesterol, mmol/L</td>
<td>1.37±0.36</td>
<td>1.32±0.31</td>
<td>1.22±0.31</td>
<td>1.24±0.36</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-Cholesterol, mmol/L</td>
<td>3.52±1.04</td>
<td>3.52±1.06</td>
<td>3.78±0.98</td>
<td>3.63±1.22</td>
<td>NS</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>3.0±0.8</td>
<td>2.9±0.7</td>
<td>3.0±0.7</td>
<td>29±0.9</td>
<td>NS</td>
</tr>
<tr>
<td>NaU, mEq/L</td>
<td>158±70</td>
<td>165±70</td>
<td>170±77</td>
<td>168±66</td>
<td>NS</td>
</tr>
<tr>
<td>Prevalence of metabolic syndrome, %</td>
<td>21</td>
<td>13</td>
<td>21</td>
<td>32</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Data are mean±SD or percentage. SUA indicates serum uric acid; BMI, body mass index; HDL, high density lipoproteins; LDL, low density lipoproteins. *P<0.05 significance as compared to the lowest serum uric acid tertile.

Statistical Analysis

All data are expressed as mean±SD. One-way analysis of variance (ANOVA) with Bonferroni or Turkey multiple comparison post-test (as appropriate) was used to analyze data from patients with different levels of serum uric acid, and with or without TOD. Relations among variables were assessed using linear regression analysis and Pearson correlation coefficient. Comparisons of proportion among groups were performed using the χ² test. Logistic regression analysis was performed to assess the independent contribution of several variables, including SUA, to the presence of TOD. All statistical analyses were performed using Statview for Windows (SAS Institute Inc, version 5.0.1, Cary, NC). P<0.05 was considered statistically significant.

Results

The main clinical characteristics of our study patients (age range, 20 to 67 years), analyzed on the basis of gender and SUA levels (tertiles), are reported in Table 1. The overall prevalence of left ventricular hypertrophy, carotid abnormalities, and microalbuminuria was 46%, 31%, and 12%, respectively. The prevalence of carotid plaque was 23%. As expected, men showed significantly higher SUA levels as compared with women (348±72 versus 246±60 μmol/L; P<0.0001). Furthermore, there was a trend toward higher body mass index (BMI), triglycerides, and prevalence of MS with growing tertiles of SUA in men. Women in the upper (SUA) tertile were older and showed higher BMI and lower creatinine clearance.

Univariate analysis showed that among the whole group, SUA was directly related to BMI, creatinine, triglycerides, low-density lipoprotein cholesterol, and the components of MS, whereas it was inversely related to high-density lipoprotein cholesterol. These associations were also present in men, whereas in women only a positive correlation with age and BMI and a negative correlation with estimated creatinine clearance were observed. SUA was unrelated to blood pressure components, alcohol consumption, and urinary sodium excretion. There was a significant linear trend for the relation between SUA levels and TOD in the whole group, because
SUA was directly related to left ventricular mass index and the severity of TOD. Taking each gender into consideration separately, the correlation was stronger in women: the higher the level of SUA, the higher the left ventricular mass index and the number of TOD that occurred. In contrast, the association between SUA and TOD was not confirmed in men (Table 2). Overall, patients with TOD had significantly higher levels of SUA as compared with those without it (Figure 1).

There was no difference in the prevalence and severity of TOD among the tertiles of SUA in men (data not shown). Conversely, in women the occurrence of each TOD we examined increased progressively from the lower to the upper tertiles (Table 3). Furthermore, females in the top tertile of SUA showed higher urinary albumin excretion and thicker carotid walls (F = 4.3, P = 0.015 intergroup comparison) (Table 3). Finally, the severity of TOD, ie, the number of organs involved, also increased from lower to upper SUA tertile in women. In fact, female patients in the highest tertile were almost 6-times more likely to show at least 2 signs of TOD as compared with those in the lowest tertile (Figure 2).

The independent relationship of SUA to the presence and severity of early organ damage was confirmed by the results of multiple logistic regression analysis (Table 4). In fact, even after adjustment for several known risk factors, such as BMI, age, creatinine clearance, and high-density lipoprotein cholesterol, each 60-mol/L increase in SUA (ie, 1 SD) entailed a 75% higher risk of having LVH and a 2-times greater risk of having carotid abnormalities. The occurrence of any one sign of TOD also increases in parallel with the elevation of SUA (Table 4). Preliminary data on ultrasound Doppler intrarenal resistive index (gathered on a subgroup of 200 patients) indicate a correlation between renovascular impedance and SUA in women (n = 76; r = 0.26; P < 0.007).

**Discussion**

The present study demonstrates that SUA levels are associated with preclinical TOD, namely LVH, carotid atherosclerosis, and microalbuminuria, in a large group of untreated patients with primary hypertension, regardless of other known cardiovascular risk factors.

Although several longitudinal studies have previously shown an independent prognostic role of SUA in hypertensive patients, to date, cross-sectional reports on the

**Table 2. Univariate Correlation Between Serum Uric Acid and Selected Clinical Variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>All</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>P</td>
<td>r</td>
</tr>
<tr>
<td>Age</td>
<td>0.03</td>
<td>NS</td>
<td>-0.04</td>
</tr>
<tr>
<td>BMI</td>
<td>0.35</td>
<td>&lt;0.001</td>
<td>0.23</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>0.44</td>
<td>&lt;0.001</td>
<td>0.18</td>
</tr>
<tr>
<td>Creat Clear</td>
<td>0.06</td>
<td>NS</td>
<td>-0.09</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.29</td>
<td>&lt;0.001</td>
<td>0.25</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.12</td>
<td>0.03</td>
<td>0.045</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>-0.27</td>
<td>0.02</td>
<td>-0.13</td>
</tr>
<tr>
<td>MS components</td>
<td>0.2</td>
<td>&lt;0.001</td>
<td>0.25</td>
</tr>
<tr>
<td>LVMI</td>
<td>0.17</td>
<td>0.002</td>
<td>-0.03</td>
</tr>
<tr>
<td>No. of organ involved</td>
<td>0.16</td>
<td>0.02</td>
<td>0.14</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; Creat Clear, estimated creatinine clearance; LDL, low density lipoproteins; HDL, high density lipoproteins; MS components, No. of metabolic syndrome components; LVMI, left ventricular mass index.

**Figure 1.** Serum uric acid and target organ damage in patients with essential hypertension (n = 425). SUA levels are analyzed on the basis of the presence/absence of different signs of TOD (1a) and on the severity of TOD involvement (1b). SUA indicates serum uric acid; LVH(echo), left ventricular hypertrophy by echocardiography; Carotid ATS, carotid atherosclerosis by US carotid scan; TOD 0, patients without signs of organ damage; TOD +, subgroup of patients with either LVH or carotid abnormalities or microalbuminuria; TOD ++, patients with a combination of any two signs of TOD; TOD ++++, those with all three signs of the TOD we examined. *P < 0.05 and †P < 0.01 vs patients without damage; ‡P < 0.01 refers to inter-group comparison.
association between mild hyperuricemia and TOD have been scanty. To our knowledge, the present study is the first to systematically investigate the relationship between SUA and cardiovascular and renal abnormalities, ie, LVH, carotid atherosclerosis, and microalbuminuria in patients with primary hypertension. Our findings suggest that uric acid may be implicated in the early pathogenetic stages of cardiovascular damage. They also provide a pathophysiological rationale to at least partly account for the association of uric acid to cardiovascular events and mortality in hypertensive patients. In fact, subclinical TOD represents an intermediate step between exposure to risk factors and occurrence of overt cardiovascular disease and has previously been shown to be a strong predictor of major events. Our study population is especially well-suited for a similar observation because most patients had received some form of therapy, albeit discontinuously, in the past. Furthermore, great care was taken to exclude patients who were taking drugs that interfere with uric acid levels and/or those with a history of gout or renal stones.

The strong correlation we observed between SUA and TOD in women (Table 3), confirms previous studies that showed a more robust association (of uric acid) with electrocardiographic abnormalities and coronary atherosclerosis in this gender. These findings may in turn account for the previously reported stronger predictive power of uric acid in women, with or without hypertension, as compared with men. In the present study, TOD involvement increased along with SUA tertiles in females (Figure 2) and was independent of several confounders such as age, serum lipid profile, blood pressure, and creatinine clearance (Table 4). Thus, it could be

**TABLE 3. Prevalence and Severity of Target Organ Damage in Hypertensive Women on the Basis of SUA Levels**

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Females</th>
<th>SUA Tertiles</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>I</td>
<td>II</td>
</tr>
</tbody>
</table>
| No.                            | 160         | 54           | 52    | 54   | 0.006*
| Prevalence of LVH -ECG,%       | 13          | 7            | 9     | 27   | NS
| Left ventricular mass index, g/m² | 114±28      | 106±26       | 112±27 | 118±29 | NS
| Prevalence of Mi, %            | 7           | 10           | 9     | 18   | 0.004*
| Carotid IMT, mm                | 0.68±0.19   | 0.65±0.16    | 0.66±0.22 | 0.75±0.20 | 0.015*
| Prevalence of carotid abnormalities, % | 30        | 19           | 23    | 48   | 0.001*
| Prevalence of LVH -echo,%      | 43          | 27           | 42    | 51   | 0.03*
| ACR mmol/mg                    | 1.3±2.7     | 0.7±0.5      | 1.5±3.2 | 2.0±3.9 | 0.02†

Data are mean±SD or percentage. LVH indicates left ventricular hypertrophy; ECG, electrocardiogram; Mi, microalbuminuria; echo, echocardiogram; IMT, intima-media thickness; ACR, urinary albumin to creatinine ratio.

*P for trend; †P III vs I SUA tertile.

LVH-ECG, χ² = 7.6; LVH-echo, χ² = 7.4; Mi, χ² = 8.2; carotid ATS, χ² = 10.8.

**TABLE 4. Multiple Logistic Regression Analysis**

4A. Dependent Variable: LVH (echo)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Difference (SD)</th>
<th>Relative Risk 95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUA 60 μmol/L</td>
<td>1.75</td>
<td>1.05–2.90</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Also in the model: age, creatinine clearance, HDL-cholesterol, mean blood pressure, fasting serum glucose not significantly related to the presence of LVH

4B. Dependent Variable: Carotid Abnormalities

<table>
<thead>
<tr>
<th>Variable</th>
<th>Difference (SD)</th>
<th>Relative Risk 95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUA 60 μmol/L</td>
<td>2.20</td>
<td>1.18–4.11</td>
<td>0.013</td>
</tr>
<tr>
<td>Age 8.3 years</td>
<td>2.34</td>
<td>1.11–4.86</td>
<td>0.024</td>
</tr>
<tr>
<td>HDL cholesterol − 0.38 mmol/L</td>
<td>1.53</td>
<td>1.18–3.81</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Also in the model: BMI, creatinine clearance not significantly related to the presence of carotid abnormalities

4C. Dependent Variable: At Least 1 TOD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Difference (SD)</th>
<th>Relative Risk 95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUA 60 μmol/L</td>
<td>2.03</td>
<td>1.06–3.84</td>
<td>0.03</td>
</tr>
<tr>
<td>BMI 3.85 kg/m²</td>
<td>3.06</td>
<td>1.65–5.90</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

Also in the model: creatinine clearance, age, HDL-cholesterol not significantly related to the presence of TOD

*Relationship of selected variables to the presence of cardiovascular TOD in female HT patients. TOD indicates sign of target organ damage; HT, hypertensive; LVH (echo), left ventricular hypertrophy detected by echocardiogram; SD, standard deviation; SUA, serum uric acid; HDL, high density lipoprotein; BMI, body mass index.

![Figure 2](https://www.ahajournals.org/doi/abs/10.1161/HYPERTENSIONAHA.105.008532)

**Figure 2.** Prevalence of increasing organ involvement in hypertensive women on the basis of SUA tertiles. SUA indicates serum uric acid; 1 affected organ indicates the subgroup of patients with either LVH or carotid abnormalities or microalbuminuria; 2 or 3 affected organs indicates patients with a combination of any two or three signs of target organ damage we examined (χ² 11.95 P < 0.018). The odds ratio of women in the third tertile having at least 2 signs of TOD is 5.5 (CI 1.2–7.3; P < 0.03).
speculated that the role of SUA as a marker of risk becomes more evident in the context of a lower risk profile (ie, in women). A similar interpretation has been put forward to justify results from the Syst-China study, which found that cardiovascular and stroke mortality increased in parallel with higher levels of SUA in elderly patients with isolated systolic hypertension but who were otherwise at relatively low risk. Furthermore, interaction between sex hormones and pathophysiological mechanisms linking SUA to cardiovascular damage cannot be ruled out. In fact, it has been proposed that the higher SUA levels observed in men as compared with women may be caused by increased renal clearance of urate related to estrogen in premenopausal women.

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. In the context of primary hypertension, mild hyperuricemia is often a feature of insulin resistance and the metabolic syndrome. As a matter of fact, we observed that higher SUA values in men were associated to an increasing number of MS components (Table 2), and more frequently to MS itself ($\chi^2=7.4, \ P=0.006$; Table 1). After adjusting for selected well-known risk factors (namely blood pressure, serum cholesterol, triglycerides, and number of MS components), we found a statistically relevant relationship between uric acid and the severity of organ damage (ANOVA F4.1; $P<0.019$ data not shown). This is partly at variance with data previously reported in the ARIC study, performed on a large group of patients who were free of overt cardiovascular disease, in which the role of SUA as a risk factor for carotid abnormalities was substantially weakened after adjustment for variables linked to MS and atherosclerosis. In women, however, we found that the relationship between uric acid and TOD was independent of the MS, because its components were equally distributed among tertiles of SUA (data not shown).

Several mechanisms have been proposed to account for the association between SUA and cardiovascular and renal abnormalities, and include: (1) increased uric acid production to counteract oxidative stress and endothelial damage in the context of the atherosclerotic process, (2) the severity of hypertension itself, and (3) a subtle reduction in glomerular filtration rate leading to impaired renal uric acid clearance. However, among our patients, we found no differences in blood pressure on the basis of SUA tertiles (Table 3), and no relationship was present between uric acid levels and any blood pressure components (data not shown). Furthermore, although the correlation we observed between uric acid and TOD was at least partly independent of the glomerular filtration rate (Table 4), women included in the upper SUA tertile also showed lower calculated glomerular filtration rate (Table 1). Johnson et al previously proposed that even mild hyperuricemia might exert nephotoxic effects by inducing vascular smooth muscle cell proliferation at the preglomerular level. This could lead to ischemia, especially in the context of long-standing hypertension. Interestingly, among our female study patients whose renal resistive index was evaluated by ultrasound Doppler, we observed an association between increased renovascular impedance and uric acid ($P<0.007$). This may indicate the presence of hemodynamic abnormalities in hypertensive patients with mild hyperuricemia. Although the cross-sectional design of our study does not allow us to draw conclusions regarding the pathogenetic mechanisms underlying these associations, these findings further support the role of SUA as a marker of renal damage.

**Perspectives**

The issue of mild hyperuricemia and cardiovascular disease has been getting more and more attention since antihypertensive agents were shown to possibly induce subtle but significant changes in uric acid, which could impact on their ability to provide cardiovascular and renal protection. However, we cannot rule out the possibility that the more favorable outcome that is observed as SUA changes over time might merely be a reflection of other factors, such as improved insulin resistance or a slight amelioration in renal function.

In conclusion, our study shows that increased SUA is a marker of subclinical TOD in a population of untreated patients with primary hypertension. These results support a role for SUA as an independent, modifiable marker of TOD. Further studies are needed to ascertain whether SUA reduction per se confers cardiovascular protection, and the possible role it may play as a surrogate end point of antihypertensive treatment.

**Acknowledgments**

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