Serum Uric Acid Levels and Risk for Vascular Diseases in Patients with Metabolic Syndrome

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ABSTRACT. Objective. Gout and increased serum uric acid (SUA) levels are often seen in patients with components of the metabolic syndrome. Increased SUA levels are associated with increased vascular risk, as is the metabolic syndrome. We investigated the association between SUA levels and the metabolic syndrome in a population of patients with manifest vascular disease to determine whether SUA levels convey an independent risk for vascular disease in patients with the metabolic syndrome.

Methods. A nested case-cohort study of 431 patients with 220 cases with a new vascular event during followup, originating from the Second Manifestations of Arterial Disease (SMART) study. All patients had manifest vascular diseases, consisting of cerebral, coronary, or peripheral artery disease or abdominal aortic aneurysm. The relationship of SUA with the metabolic syndrome was analyzed with linear regression and adjusted for age, sex, creatinine clearance, and alcohol and diuretic use. The relationship of SUA levels with new vascular disease was investigated with Cox regression and adjusted for age and sex.

Results. The metabolic syndrome was present in 50% of patients. SUA levels were higher in 214 patients with the metabolic syndrome than in 217 patients without (0.36 ± 0.08 mmol/l vs 0.32 ± 0.09 mmol/l). SUA concentrations increased with the number of components of the metabolic syndrome (0.30 mmol/l to 0.38 mmol/l) adjusted for age, sex, creatinine clearance, and alcohol and diuretic use. Increased SUA concentrations were independently associated with risk for vascular events in patients without the metabolic syndrome (age and sex adjusted hazard ratio 2.4, 95% CI 1.0–5.5), in contrast to patients with the metabolic syndrome (adjusted hazard ratio 1.9, 95% CI 1.0–3.9).

Conclusion. Elevated SUA levels are strongly associated with the metabolic syndrome, yet are not an independent risk factor for vascular disease in patients with the metabolic syndrome. In patients without the metabolic syndrome, elevated SUA levels are associated with increased risk for vascular disease. (First Release August 1 2007; J Rheumatol 2007;334:1882–7)

Key Indexing Terms:
SERUM URIC ACID VASCULAR DISEASE METABOLIC SYNDROME EPIDEMIOLOGY

Clustering of vascular risk factors associated with central obesity is often referred to as the metabolic syndrome1,2, which is associated with an increased risk for the development of vascular disease, which could be explained by the individual components of the metabolic syndrome1,3,4. Although the exact underlying pathophysiology of the metabolic syndrome remains unclear, insulin resistance has been found to play a major role5. Serum uric acid (SUA) is elevated in an insulin-resistant state, and increased levels of uric acid are associated with vascular disease6-10. It could therefore be hypothesized that increased SUA contributes to the increased risk for the development of vascular disease in patients with the metabolic syndrome. On the other hand, gout and increased SUA levels are typically seen in middle-aged, overweight patients with hypertension and hyperlipidemia, all components of the metabolic syndrome11, and these have recently been shown to be an independent risk factor for myocardial infarction12. It is unknown whether increased SUA levels further increase the elevated vascular risk in these patients with metabolic syndrome, and which component of this syndrome is most closely associated with increased SUA levels and gout.

Uric acid is the final breakdown product of dietary and endogenous purines and is generated by xanthine dehydrogenase (xanthine oxidase), primarily in the liver and intestine13. The relationship of SUA with vascular disease may be explained by several pathophysiological mechanisms, including oxidative stress, inflammation, endothelial dysfunction,
and platelet adheriveness, which are all involved in atherogenesis. In addition, an elevated SUA level may elevate blood pressure, because of its effects on the renal interstitium.

SUA is associated with established vascular risk factors such as hypertension, obesity, low levels of high-density lipoprotein cholesterol, hypertriglyceridemia, hyperinsulinemia, and impaired glucose tolerance, which are all involved in the metabolic syndrome. It has been proposed that the attendant compensatory hyperinsulinemia caused by insulin resistance may contribute to the pathogenesis of hyperuricemia through its renal effect.

Controversy surrounds the role of SUA in vascular disease. Whether the relationship of SUA with vascular events is causal or interdependent or is merely an epiphenomenon remains unclear. Epidemiological studies have shown that elevated SUA levels are a strong predictor of increased risk of vascular events, although an independent relationship has been refuted by other studies.

We investigated the associations of SUA levels with individual components of the metabolic syndrome and explored whether an elevated SUA level is an independent risk factor for vascular disease in patients with manifest vascular disease, with and without the metabolic syndrome.

MATERIALS AND METHODS

Study population. For this nested case-cohort study, data were used from patients enrolled in the Second Manifestations of Arterial Disease (SMART) Study, an ongoing prospective cohort study at the University Medical Center Utrecht, designed to establish the prevalence of comitant arterial diseases and risk factors for vascular disease in a high-risk population. The Medical Ethics Committee approved the study and all subjects gave their written informed consent before participating.

We examined data for 431 patients with clinical manifest arterial disease. Coronary artery disease included angina pectoris and myocardial infarction; cerebral vascular disease included transient ischemic attack, cerebral infarction, amaurosis fugax, and retinal infarction; peripheral artery disease included symptomatic and documented obstruction of distal arteries of the leg (Fontaine II and III) or abdominal aortic aneurysm. A total of 2398 patients with a history of vascular disease were enrolled in the SMART study between 1996 and 2003; 220 cases emerged who had had a new vascular event during followup. A random sample of 240 patients (10%) was drawn from the 2398 patients and served as a reference control group. Of these 240 patients, 16 had already been selected because of an outcome event. Hence, the study population consisted of 444 patients. Because blood samples of 13 patients were missing, analyses were carried out with the data of 431 patients.

Definitions. At the time of enrollment, clinical information was obtained with a standardized health questionnaire. Height, body weight, waist circumference, and blood pressure were measured. Fasting blood was sampled to determine lipid, serum glucose, creatinine, adiponectin, insulin, and uric acid concentrations. SUA levels were measured with an immunochemical assay (Vitros 250 Chemistry System, Johnson & Johnson Clinical Diagnostics, Rochester, NY, USA). Reference values for serum, male: 0.20–0.44 mmol/l; female: 0.14–0.34 mmol/l. Measurable range from 0.03 mmol/l to 1.01 mmol/l.

Metabolic syndrome was diagnosed according to the Adult Treatment Panel III criteria, including 3 or more of the following abnormalities: abdominal obesity (waist circumference > 102 cm in men and > 88 cm in women), high blood pressure (≥ 130 mm Hg systolic or ≥ 85 mm Hg diastolic), and use of blood pressure-lowering agents, hypertriglyceridemia [serum triglycerides ≥ 1.70 mmol/l (150 mg/dl)], low HDL cholesterol [serum HDL cholesterol < 1.04 mmol/l (40 mg/dl) in men and < 1.29 mmol/l (50 mg/dl) in women], and high fasting glucose [fasting serum glucose ≥ 6.1 mmol/l (110 mg/dl) or use of glucose-lowering agents]. Waist circumference was measured in participants entering SMART before January 1, 1999. If waist circumference was not available, a body mass index cutpoint of 30 kg/m² was used as criterion for obesity. Diabetes was defined as self-reported diabetes or the use of glucose-lowering agents or a fasting glucose ≥ 7.0 mmol/l in patients with no history of diabetes. History of vascular disease included atherosclerotic vascular diseases in the medical history other than the vascular diagnosis at inclusion. Current or past smoking included patients currently smoking and those who recently stopped or smoked in the past. A similar definition was used for current or past alcohol drinking. Renal function was determined with the Cockcroft-Gault formula. Homeostasis model assessment of insulin resistance (HOMA-IR) was used as quantitative estimate of insulin resistance.

Patients were asked biannually to complete a questionnaire on hospitalizations and outpatient clinic visits. Events of interest for this study were the occurrence of a composite of first vascular events, namely vascular death, ischemic stroke, and coronary ischemic event.

When a possible event was reported by the patient, hospital discharge letters and results of relevant laboratory and radiology examinations were collected. Based on this information, all events were audited by 3 members of the SMART study endpoint committee. This consisted of physicians from different departments. In case of disagreement, consensus was reached by consulting other members of the endpoint committee.

Data analyses. Data are presented as percentages with number of patients, as mean ± standard deviation for normally distributed variables, and as median with interquartile range for non-normally distributed variables. Multiple linear regression analysis was performed to investigate the association of SUA with the metabolic syndrome and the relation of SUA with the number of metabolic syndrome components. The presence of the metabolic syndrome was taken as the dependent variable and SUA levels as independent; the relationships were adjusted for sex, age, renal function (Cockcroft-Gault), and alcohol and diuretic use. Cox proportional hazard regression models were used to investigate the relation of SUA levels with new vascular events in patients with and without the metabolic syndrome. Endpoint hazard ratio (HR) for each uric acid category was calculated with the lowest uric acid category as reference in patients without the metabolic syndrome. Results are presented as HR with corresponding 95% confidence intervals (CI); effect estimates were adjusted for age and sex. All statistical analyses were performed using the Statistical Package for the Social Sciences for Windows 11.1 (SPSS, Chicago, IL, USA), except for the Cox regression, which was performed using SAS.

RESULTS

Study population. Baseline characteristics of the study population are presented in Table 1 according to tertiles of SUA. We identified 217 (50%) patients with metabolic syndrome and 214 (50%) patients without. Based on a cutoff point of 7.0 mg/dl (0.416 mmol/l), 32 (15%) patients without the metabolic syndrome and 52 (24%) with metabolic syndrome had hyperuricemia. Patients with the metabolic syndrome had a higher creatinine clearance (73 vs 70 ml/min). Differences were noted in fasting serum glucose concentrations (6.6 vs 5.5 mmol/l), adiponectin levels (4.2 vs 6.0 µg/l), higher triglycerides (2.33 vs 1.23 mmol/l), and lower HDL-cholesterol levels (0.94 vs 1.26 mmol/l) in patients with compared to those without the metabolic syndrome. At baseline, previous clinical manifestations of atherosclerotic disease were equally distributed in both groups. Use of diuretics and use of other blood-pressure-lowering medications were more frequently seen in patients with the metabolic syndrome.
Relation between uric acid plasma levels and the metabolic syndrome. The relationship between uric acid and the metabolic syndrome is described in Table 2. The crude difference in uric acid levels between patients with and without the metabolic syndrome was 0.04 mmol/l (95% CI 0.02–0.06). Adjusting for age, sex, creatinine clearance, and use of alcohol and diuretics did not change these values essentially. We observed a gradual increase of SUA levels parallel to an increase in the number of components of the metabolic syndrome, in both crude and adjusted analyses.

Table 3 shows the relation between the individual components of the metabolic syndrome and uric acid. In particular, waist circumference (0.37 ± 0.09 vs 0.33 ± 0.09) and triglyceride levels (0.37 ± 0.08 vs 0.32 ± 0.09) were significantly associated with elevated uric acid levels after multiple adjustments.

Uric acid and new vascular events in patients with and without metabolic syndrome. The mean (± SD) SUA concentrations of each of these tertiles were 0.25 ± 0.04, 0.33 ± 0.02, and 0.44 ± 0.07 mmol/l, respectively (Table 1). Age was equally distributed. The creatinine clearance decreased from 76 ± 20 to 74 ± 26 to 64 ± 24 ml/min from Tertile One to Tertile Three, respectively. Differences were seen in adiponectin levels (6.0 vs 5.0 vs 4.8 µg/ml), triglycerides (1.48 vs 1.67 vs 1.85 mmol/l), HDL-cholesterol (1.25 vs 1.05 vs 1.04 mmol/l), and waist circumference (91 vs 98 vs 100 cm). The use of diuretics and other blood pressure-lowering agents was seen predominantly in Tertile Three.

In patients without the metabolic syndrome there was an increase in HOMA-IR over the 3 tertiles of uric acid (mean ± SD: 2.4 ± 2.3, 2.6 ± 2.0, and 3.1 ± 3.4). In patients with the metabolic syndrome there seems to be a clear increase in insulin resistance only in the third tertile (mean ± SD: 4.5 ± 2.6, 4.6 ± 2.6, and 5.5 ± 5.3, respectively; Table 1). In patients who did not have the metabolic syndrome, the adjusted hazard ratios for a vascular event are for Tertile Two 1.9 (95% CI 0.9–3.8) and for Tertile Three 2.4 (95% CI 1.0–5.5); Tertile One is reference (Table 4). In patients with

### Table 1. Baseline laboratory findings of study population based on uric acid tertiles.

<table>
<thead>
<tr>
<th>Variable</th>
<th>1, n = 133</th>
<th>2, n = 155</th>
<th>3, n = 142</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum uric acid, mmol/l&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.25 ± 0.04</td>
<td>0.33 ± 0.02</td>
<td>0.44 ± 0.07</td>
</tr>
<tr>
<td>Male, %</td>
<td>61</td>
<td>80</td>
<td>86</td>
</tr>
<tr>
<td>Age, yrs&lt;sup&gt;a&lt;/sup&gt;</td>
<td>62 ± 11</td>
<td>61 ± 11</td>
<td>64 ± 10</td>
</tr>
<tr>
<td>Body mass index, kg/m²&lt;sup&gt;a&lt;/sup&gt;</td>
<td>25 ± 4</td>
<td>27 ± 4</td>
<td>27 ± 4</td>
</tr>
<tr>
<td>Smoking*, %</td>
<td>87</td>
<td>76</td>
<td>86</td>
</tr>
<tr>
<td>Alcohol drinking**&lt;sup&gt;, %&lt;/sup&gt;</td>
<td>73</td>
<td>75</td>
<td>81</td>
</tr>
<tr>
<td>Creatinine clearance (Cockroft), ml/min&lt;sup&gt;a&lt;/sup&gt;</td>
<td>76 ± 20</td>
<td>74 ± 26</td>
<td>64 ± 24</td>
</tr>
<tr>
<td>Fasting serum insulin, mIU/l&lt;sup&gt;b&lt;/sup&gt;</td>
<td>9 (7–13)</td>
<td>13 (8–18)</td>
<td>13 (9–19)</td>
</tr>
<tr>
<td>Adiponectin, µg/ml&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6.0 (3.6–8.9)</td>
<td>5.0 (3.4–7.9)</td>
<td>4.8 (3.1–7.8)</td>
</tr>
<tr>
<td>Use of lipid-lowering agents, %</td>
<td>42</td>
<td>37</td>
<td>36</td>
</tr>
<tr>
<td>Use of glucose-lowering agents, %</td>
<td>21</td>
<td>21</td>
<td>22</td>
</tr>
</tbody>
</table>

HOMA-IR<sup>†</sup>

- With metabolic syndrome: 2.4 ± 2.3, 2.6 ± 2.0, 3.1 ± 3.4
- Without metabolic syndrome: 4.5 ± 2.6, 4.6 ± 2.6, 5.5 ± 5.3

Use of blood pressure-lowering agents

- Diuretics, %: 6, 14, 32
- Calcium antagonists, %: 22, 23, 24
- ACE inhibitors, %: 22, 19, 31
- Beta-blockers, %: 35, 41, 46

Manifest vascular disease at baseline

- Peripheral artery disease, %: 34, 25, 32
- Cerebral vascular disease, %: 38, 35, 29
- Coronary artery disease, %: 45, 53, 59
- Abdominal aortic aneurysm, %: 12, 20, 22

Components of metabolic syndrome

<table>
<thead>
<tr>
<th>Glucose, mmol/l&lt;sup&gt;b&lt;/sup&gt;</th>
<th>5.7 (5.2–7.0)</th>
<th>6.0 (5.5–8.8)</th>
<th>5.9 (5.6–6.7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides, mmol/l&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.48 (1.05–1.86)</td>
<td>1.67 (1.26–2.38)</td>
<td>1.85 (1.28–2.35)</td>
</tr>
<tr>
<td>HDL-cholesterol, mmol/l&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.25 (1.05–1.46)</td>
<td>1.05 (0.91–1.32)</td>
<td>1.04 (0.88–1.23)</td>
</tr>
<tr>
<td>Waist circumference, cm&lt;sup&gt;a&lt;/sup&gt;</td>
<td>91 ± 11</td>
<td>98 ± 13</td>
<td>100 ± 10</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg&lt;sup&gt;a&lt;/sup&gt;</td>
<td>145 ± 25</td>
<td>148 ± 22</td>
<td>142 ± 20</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg&lt;sup&gt;a&lt;/sup&gt;</td>
<td>79 ± 11</td>
<td>82 ± 10</td>
<td>79 ± 11</td>
</tr>
</tbody>
</table>

<sup>a</sup> Mean ± standard deviation. <sup>b</sup> Median (interquartile range). * Percentage of cases still smoking, recently stopped smoking, or previously smoking. ** Percentage of cases still drinking, recently stopped drinking, or previously drinking. † Homeostasis model assessment of insulin resistance. ACE: angiotensin-converting enzyme.
DISCUSSION

We found that elevated SUA levels were closely associated with the metabolic syndrome in patients with manifest vascular disease, and that increased SUA levels were associated with an increased vascular risk in patients without the metabolic syndrome. Patients with the metabolic syndrome showed significantly higher SUA concentrations compared to those without.

The observation that not all the individual components of the metabolic syndrome are significantly associated with SUA, in addition to the relatively small difference in uric acid concentrations between the presence and absence of the criteria, emphasizes that the metabolic syndrome functions, and needs to be regarded, as a cluster of risk factors.

Although there are differences in uric acid levels between the presence and absence of individual metabolic syndrome criteria, waist circumference and triglycerides are the only criteria significantly related to uric acid levels in this population. This could be explained by the central role of insulin resistance. The attendant compensatory hyperinsulinemia, caused by insulin resistance, may contribute to the pathogenesis of increased serum uric acid through renal effects. One hypothesis is that the kidneys are directly affected by rising insulin levels and that urinary uric acid clearance decreases in pro-

Table 2. Relation between uric acid and metabolic syndrome (defined by the ATP III criteria).

<table>
<thead>
<tr>
<th>Metabolic syndrome</th>
<th>N</th>
<th>Uric Acid, Crude</th>
<th>Δ (95% CI)</th>
<th>Uric Acid, Adjusted for Age and Sex</th>
<th>Δ (95% CI)</th>
<th>Uric Acid Adjusted for Age, Sex, Creatinine Clearancea</th>
<th>Δ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>217</td>
<td>0.32 ± 0.09</td>
<td>—</td>
<td>0.33 ± 0.09</td>
<td>—</td>
<td>0.33 ± 0.09</td>
<td>—</td>
</tr>
<tr>
<td>Yes</td>
<td>214</td>
<td>0.36 ± 0.08</td>
<td>0.04 (0.02–0.06)*</td>
<td>0.36 ± 0.08</td>
<td>0.04 (0.02–0.06)*</td>
<td>0.36 ± 0.08</td>
<td>0.04 (0.02–0.06)*</td>
</tr>
</tbody>
</table>

Table 3. Relations between individual criteria of the metabolic syndrome (according to ATP III components) and uric acid levels.

<table>
<thead>
<tr>
<th>Waist circumference, cm</th>
<th>Crude</th>
<th>Δ (95% CI)</th>
<th>Adjusted for Age and Sex</th>
<th>Δ (95% CI)</th>
<th>Adjusted for Age, Sex, Renal Clearancea</th>
<th>Δ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>0.34 ± 0.09</td>
<td>—</td>
<td>0.34 ± 0.09</td>
<td>—</td>
<td>0.33 ± 0.09</td>
<td>—</td>
</tr>
<tr>
<td>Yes</td>
<td>0.35 ± 0.09</td>
<td>0.01 (–0.01–0.03)</td>
<td>0.36 ± 0.09</td>
<td>0.02 (–0.01–0.04)</td>
<td>0.37 ± 0.09</td>
<td>0.04 (0.02–0.06)*</td>
</tr>
</tbody>
</table>

Data are means ± standard deviation. a Cockroft-Gault formula. * p < 0.05.

the metabolic syndrome the hazard ratios are for Tertile One 1.9 (95% CI 0.8–4.2), Tertile Two 1.6 (95% CI 0.8–3.1), and Tertile Three 1.9 (95% CI 1.0–3.9), respectively. Tertile One of patients without the metabolic syndrome is used as reference.
portion to increasing insulin resistance, thus increasing SUA\textsuperscript{18}. Studies have shown that an important contributor to the development of insulin resistance is an overabundance of circulating free fatty acids\textsuperscript{9,13,18}. Plasma albumin-bound free fatty acids are derived mainly from adipose tissue triglyceride stores released through the action of the cyclic-AMP-dependent enzyme hormone-sensitive lipase\textsuperscript{13}. Obesity, measured by waist circumference and indicated by an increase in abdominal adipose tissue, contributes to higher plasma concentrations of free fatty acids\textsuperscript{18}.

Increased SUA levels are associated with elevated blood pressure, possibly through the generation of reactive oxygen species, impaired endothelial nitric oxide release, and subsequent endothelial dysfunction\textsuperscript{11}. However, even though use of diuretics was considered as a confounder in our analysis, elevated uric acid levels were not associated with the presence of the ATP-III blood pressure criterion of the metabolic syndrome. This may be due to the extensive use of blood pressure-lowering agents other than diuretics in our study population. Interestingly, although the SUA concentrations in our study fall within the range of what are considered normal plasma concentrations, there is a significant cardiovascular risk associated with elevated uric acid concentrations. Hyperuricemia is usually defined as SUA concentrations > 6.5 or 7.0 mg/dl (0.39 or 0.42 mmol/l) in men and > 6.0 mg/dl (0.36 mmol/l) in women\textsuperscript{14}.

Our study also documents that increased levels of SUA are independently associated with high vascular disease risk in patients without the metabolic syndrome, in contrast to patients with the metabolic syndrome in whom elevated SUA is not associated with an increased risk for vascular events. This may be explained by uric acid as a vascular risk factor already being accounted for by the presence of other risk factors clustering in the metabolic syndrome. SUA is so closely linked to insulin resistance that increased SUA concentrations do not lead to additional risk for vascular disease in these patients. Liao, et al documented that the ATP-III criteria show good specificity, and poor sensitivity for the presence of insulin resistance\textsuperscript{32}. This poor sensitivity of ATP-III criteria for identifying insulin resistance could indicate that a significant number of patients are insulin-resistant but do not exhibit the metabolic syndrome trait complex. Thus patients who do not meet the ATP-III criteria could still be insulin-resistant.

Insulin resistance could therefore also explain the relation of SUA to cardiovascular risk in patients with no metabolic syndrome. Moreover, in each tertile of uric acid in patients without the metabolic syndrome a gradual increase in HOMA-IR can be seen, indicating a role for insulin resistance.

In addition, because of the association of SUA to insulin resistance\textsuperscript{13} also observed in our study, one can make a case for adding elevated SUA levels as a criterion for the metabolic syndrome based on our findings. This could enable SUA to function as an additional marker within the definition of the metabolic syndrome for insulin resistance. Adding SUA to the current metabolic syndrome criteria, the predictive value for the diagnosis of insulin resistance and therefore the predictive value for new vascular disease may improve.

From our results it cannot be concluded whether SUA is a risk factor actively involved in atherogenesis or just an indicator of risk for vascular diseases. Our study population consisted of patients with clinical manifestations of arterial diseases and it is therefore unknown whether the results can be generalized to patients without clinically manifest arterial disease and non-survivors of vascular events. Although we have shown uric acid was independently associated with atherosclerotic disease in patients without the metabolic syndrome, prognostic studies are needed to assess the value of uric acid as a predictor of atherosclerotic disease in the context of other risk factors.

Elevated serum uric acid levels are strongly linked to the metabolic syndrome, but are not associated with an increased risk for vascular disease in patients with the metabolic syndrome. Increased serum uric acid levels are associated with increased risk for vascular disease in patients without the metabolic syndrome.

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